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## SYNDROME OF ANEMIA, GLOSSITIS AND DYSPHAGIA

REPORT OF EIGHT CASES, WITH SPECIAL REFERENCE TO  
OBSERVATIONS AT AUTOPSY IN ONE INSTANCE

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The association of dysphagia, superficial glossitis and anemia has been noted sufficiently frequently during the past few years to have become regarded as a clinical entity, and has often been referred to as the "Plummer-Vinson syndrome." Since none of the many hypotheses concerning the nature of this condition appears to have been based on histopathologic data, it was thought that a report of the observations at autopsy in one instance might prove of value. In addition, a review of the literature and the clinical findings in eight cases of this syndrome are presented.

The syndrome was first pointed out independently by Brown Kelly<sup>1</sup> and by D R Paterson<sup>2</sup> at the summer congress of the Laryngological Section of the Royal Society of Medicine in London, May 2, 1919, with papers entitled, respectively, "Spasm at the Entrance of the Oesophagus" and "A Clinical Type of Dysphagia."

The condition, as described by these writers, was confined to women of middle age. Anemia, dyspepsia and impaired general health were notable features and occasionally preceded the dysphagia, which, referred to the level of the larynx, had often been present for years. The onset, although usually gradual, was occasionally sudden, being first noticed when a particle of food became lodged in the throat. Although intervals of freedom from symptoms occasionally occurred early in the course of the disease, these intervals gradually diminished until the dysphagia became constant. As a result, mastication of necessity became thorough, and swallowing careful, slow and tedious, and the diet was reduced to semisolids and liquids. Frequent catching of food at the entrance to the gullet occurred, with distressing efforts to dislodge it, referred to as "choking spells." A longer time was taken at meals, what is known as

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From the Medical Services of the Massachusetts General Hospital, Boston

<sup>1</sup> Kelly, A B J Laryng & Otol 34 285, 1919

<sup>2</sup> Paterson, D R J Laryng & Otol 34 289, 1919

a "small swallow" thus developing. Becoming apprehensive and nervous for fear of choking, these patients thus preferred solitude during meals.

The mucous membrane of the mouth and tongue exhibited a smooth, glossy appearance, the latter being devoid of papillae. Fissures were present at the angles of the mouth, due, according to Kelly, to the increased salivation dependent on the esophageal obstruction (Rogers' salivary-esophageal reflex). This condition was found to have extended to the pharynx, the hypopharynx and occasionally the upper section of the gullet. In these situations the mucosa, which was pale and dry, was also very thin, special care being necessary during instrumentation to avoid producing a crack, the mucosa having lost the suppleness and resiliency which permits the cricoid being tilted forward to get a good view of the introitus. The deepest part of the hypopharynx did not present the usual sphincter-like appearance. Instead of rounded folds or cushions of mucous membrane forming a stellate arrangement, tense bands passed in various directions with their thin edges tightly pressed together. The entrance to the esophagus appeared as a pinhole or small irregular opening, or as an obliquely placed slit, and was not always in the midline. Sometimes half of the mouth of the gullet seemed closed by a web passing backward from the cricoid. Paterson noted that the buccal and tongue mucosa exhibited a thinning of the superficial epidermal layer and an apparent thickening from infiltration of the underlying tunica propria. The appearance was not unlike that of a condition due to syphilis, but negative Wassermann reactions and the failure of improvement under antisiphilitic treatment ruled out this disease. Since pressure on the folds of mucous membrane caused them to fall apart during instrumentation, Kelly was of the opinion that the stenosis was due to their firm approximation and not to organized adhesions. These writers stressed the spasmodic nature of the obstruction, and in this connection Kelly mentioned as a possible etiologic factor inflammatory involvement of the nerve supply causing hyperesthesia of the sensory side (Meissner's plexus) or stimulation of the motor side (Auerbach's plexus), both of which phenomena would lead to spasm. The tendency of cancer to supervene was pointed out, Kelly also commenting on the fact that 75 per cent of cancers of the upper end of the esophagus occur in women. Concerning the neurosis, so commonly present, Brown Kelly did not regard these patients as being primarily neurotic, since before the onset of the difficulty in swallowing they had been quite normal in this respect. Treatment consisted of the passage of an esophagoscope.

In 1922, Porter P. Vinson,<sup>3</sup> in a paper entitled "Hysterical Dysphagia," reported sixty-nine cases from the Mayo Clinic. In this

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<sup>3</sup> Vinson, P. P. *Minnesota Med* 5 107, 1922

series of patients, of whom 51 were males and 12 females, the onset of the dysphagia was usually sudden, often dating from a choking attack brought about by a piece of solid food lodged high in the throat. A moderate secondary anemia developed, thought by this writer to be due probably to the quality of the food which these patients were obliged to consume. In thirty-seven of the patients the hemoglobin content was below 60 per cent, the lowest reading being 27 per cent. Splenomegaly was noted in twelve instances. Roentgen examination of the esophagus showed nothing abnormal. It is interesting to note that in contrast to the findings of Kelly and Paterson, endoscopic examination did not reveal anything regarded as abnormal, nor were lesions of the mouth or tongue noted. Treatment consisted of the passing of a plain esophageal sound (size immaterial) into the stomach, guided by a previously swallowed silk thread, reassurance of the patient that he would be able to swallow forthwith, and the administration of iron and arsenic. Under this therapy, in addition to shrinking of the spleen, the blood picture improved at once, and became normal if the symptoms did not eventually recur—which was not unlikely if the patients were not constantly reassured with regard to their condition. Concerning the dysphagia, Vinson was of the opinion that the treatment was purely suggestive, as it entailed no real stretching of the esophagus. An interesting observation, pointed out by Plummer,<sup>4</sup> in patients who had been relieved of their dysphagia and were taking food freely, was the development of a moderate degree of hypothyroidism, which necessitated the administration of thyroxine. In explanation of this, it was suggested that during long periods of inanition a light demand for thyroxine results in atrophy of the thyroid from disuse, hence, following the relief of the dysphagia, this organ may not be able to meet the metabolic demands of the body.

In 1926, Moersch and Conner<sup>5</sup> of the Mayo Clinic, reported on sixty-five cases of this syndrome. All the patients were women between the ages of 23 and 63 years, the average being 45, they had suffered from the disease for periods varying from one month to thirty-four years, the average duration being eight years. The onset was usually sudden. Loss of weight, occurring in about half of the cases, was not marked, averaging only 8 pounds (3.6 Kg.). The mucous membrane of the mouth was atrophic and dry, and cracks at the corner of the mouth and glossitis were occasionally noted. A large number of the patients were edentulous. No organic lesions, such as webs or membranes, were noted in the esophagus, the mucous membrane of which, however, was dry, atrophic and inelastic, tending to bleed easily. Splenomegaly was noted in twenty of the sixty-five cases. The average figures for the

<sup>4</sup> Plummer, cited by Vinson.<sup>3</sup>

<sup>5</sup> Moersch, H. J., and Conner, H. M. Hysterical Dysphagia, *Arch. Otolaryng.* 4:112 (Aug.) 1926.



red blood cell counts, hemoglobin concentrations and color indexes were, respectively, 3,800,000, 48 per cent and 0.6. There were no significant alterations in the total or differential counts of the white blood cells. Of the ten instances in which a gastric analysis was performed, achlorhydria was present in eight. Paresthesia of the extremities was a feature in five cases. The treatment used by these physicians was identical with that advocated by Vinson, much importance being attached to the processes of suggestion and reassurance. They regarded the syndrome as being a fundamental disturbance primarily involving deglutition, dependent on some nervous or psychic strain, and they believed that the anemia and splenomegaly were probably the result of the prolonged unbalanced diet arising from the difficulty in swallowing. They suggested, in view of the occasional precedence in time of the anemia, glossitis and stomatitis over the dysphagia, that the latter may well be due to irritation of the entrance to the gullet by the esophagitis associated with the preexisting inflammatory lesions of the mouth. They also pointed out some similarity of this disease to pernicious anemia, and suggested that both diseases may have a common fundamental deficiency factor.

In 1926, A. F. Hurst<sup>6</sup> reported a single case, in which the anemia antedated the difficulty in swallowing by two years. Paresthesia, splenomegaly and a "streptococcal glossitis" were present. The anemia was microcytic and hypochromic, the average diameter of the red blood cells being 6.82 microns and the color index below unity. Roentgen examination revealed considerable hesitation in the passage of food from the pharynx into the esophagus. It was impossible to pass an esophagoscope or mercury bougie owing to tight spasm of the sphincter. The patient improved considerably on the administration of iron, although the dysphagia did not disappear entirely. This writer was of the opinion that the anemia and splenomegaly were due to the streptococcal infection rather than the result of an unbalanced diet dependent on the dysphagia, and further, that the latter was due to a reflex spasm caused by local inflammation produced by the same streptococcal infection which led to glossitis.

Ryle,<sup>7</sup> in 1928, reported a case of esophageal spasm with severe anemia, the onset of which took place shortly after a confinement. Recurrent superficial ulceration of the tongue was a feature, but there were no organic lesions in the throat. The dysphagia was relieved by esophagoscopy, and the anemia by the administration of iron and arsenic. The writer was of the opinion that the difficulty in swallowing was hysterical, that the anemia had been initiated by sepsis associated

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6 Hurst, A. F. *Guy's Hosp. Rep.* **76** 426, 1926.

7 Ryle, J. A. *Guy's Hosp. Rep.* **77** 33, 1927.

with the confinement and was perpetuated by the poor diet, and that the condition of the tongue was that of a streptococcal glossitis

Jones and Owen,<sup>8</sup> in 1928, reported on a series of cases, the findings in which were essentially similar to those described by previous writers, including a normal white blood cell picture. They confirmed the esophageal appearances noted by Kelly and Paterson, stating that the lumen of the intestine may be greatly reduced by a thin membranous web or that tense bands of raised thinned mucosa may pass in various directions. They pointed out, however, that the esophageal opening was occasionally very lax with no sphincter-like action. The x-ray findings presented nothing of note except an occasional slight hesitation in the passage of food into the esophagus. These writers were of the opinion that sepsis was not an etiologic factor.

In 1929, Cameron,<sup>9</sup> in a report of twenty-five cases, all of which were in women between the ages of 41 and 60 years, described the usual buccopharyngeal and blood findings. He noted that hydrochloric acid was present in the stomach in all of the eleven patients on whom a gastric analysis was performed, and that splenomegaly was not an infrequent finding. In regard to the sequence of the symptoms, he noted that in fifteen cases dysphagia preceded the pallor, while in five instances the latter was noticed before the onset of the difficulty in swallowing, in the remaining five cases this point was difficult to decide. The anemia, he suggested, was probably the result of lack of iron associated with the semistarvation brought about by the dysphagia. This writer also thought that perhaps the cause of the difficulty in swallowing may be found in involvement of the nerve endings brought about by inflammatory changes in the mucosa and submucosa. Atrophy of the mucous glands was also cited as a contributing factor. Attention was drawn to the high incidence of cancer at this site in women, and also to the occasional supervention of malignant disease at the entrance to the gullet in this syndrome. Treatment consisted of passing an esophageal dilator and the administration of iron and occasionally of thyroid extract.

Evans,<sup>10</sup> in a paper entitled "Nervous Dysphagia," put forward the view that the underlying cause of this syndrome is tertiary syphilis of the third or fourth generation. To substantiate this hypothesis, this writer cited the occurrence of symptoms of involvement of the central nervous system, cardiovascular changes, such as tachycardia or arrhythmia, and, in addition, lesions of the lips, mouth and tongue, an occasional positive Wassermann reaction and the beneficial effect of antisyphilitic treatment.

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8 Jones, A. M., and Owen, R. D. *Brit. M. J.* 1:256, 1928.

9 Cameron, M. J. *Laryng. & Otol.* 44:168, 1929.

10 Evans, G. *Practitioner* 124:317, 1930.

Recently, Witts,<sup>11</sup> in addition to a short review of the literature, reported the findings of this syndrome in thirteen instances, all in middle-aged women, with a mean duration of symptoms of approximately thirteen years. In nine cases the three cardinal symptoms developed simultaneously, in three dysphagia appeared first, while in one the anemia was a feature many years before the onset of the difficulty in swallowing. The usual buccopharyngeal manifestations were also noted. With one exception, the anemia was of the microcytic type throughout, the average figures for red and white blood cell counts, hemoglobin concentration and color index were, respectively, 4,200,000, 7,200, 48 per cent and 0.55. Although the differential white blood cell count, the blood platelet count, the fragility of the red blood cells and the number of reticulocytes were normal, the Arneht counts were noted as having shown a "shift to the left." This condition of the leukocytes tended to disappear coincidently with the improvement in the hemoglobin concentration. One patient was trephined over the upper third of the tibia, but only fatty marrow was obtained. Splenomegaly, present in five of the thirteen patients, disappeared in four during treatment. Of seven patients, only one had a normal gastric secretion, three had complete achlorhydria, one a low amount of free hydrochloric acid and one only a trace. In the remaining case, it is interesting to note that, although achlorhydria and macrocytic anemia were originally present, in a relapse three years later some free hydrochloric acid was found in the gastric contents and the anemia had become microcytic. An important observation in another case was a relapse of the anemia, unaccompanied by a recurrence of dysphagia, after an initial recovery from both these symptoms. Witts treated his patients with iron in large doses and occasionally with transfusion of blood and the passage of esophageal bougies. Administration of liver and diluted hydrochloric acid or of preparations of vitamins B or A, C and D did not seem to influence the anemia, glossitis or dysphagia. The anemia was relatively easily alleviated with iron and then dysphagia became more tolerable and the glossitis usually improved. This writer pointed out the occasional occurrence of mild dysphagia in what he called simple achlorhydric anemia, and the close correspondence of the latter disease with the present syndrome in regard to the age and sex of the patient and to the glossitis and anemia. Other conditions were mentioned, such as sprue, pellagra, chylous diarrhea, stenosis of the small intestine and Addisonian pernicious anemia, in which glossitis, anemia and occasionally dysphagia are found. He did not believe that this disease was a result of streptococcal infection (Hurst), that the anemia was due to the dysphagia (Vinson) or that the symptoms were the result of syphilis (Evans).

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11 Witts, L. J. *Guy's Hosp. Rep.* **81** 193, 1931

Recently, Paterson,<sup>12</sup> in a communication to the Royal Society of Medicine, confirmed his original observation and views on this subject. His description of the syndrome was essentially similar to that reported in 1919. This writer retained the view that the obstruction is of the nature of a spasm, and that the anemia is a late symptom, secondary to the dysphagia. He stated, however, that from an early stage in the course of the disease some degree of atrophic change may be noted in the mucous membrane of the tongue. Concerning treatment, in addition to instrumentation, the importance of reassurance to the patient regarding the swallowing of solid food was noted. He stressed the frequency with which malignant growths develop in this syndrome.

In the discussion of Paterson's<sup>12</sup> paper, R. S. Johnson pointed out from his experience with six cases that following the passage of bougies, although dysphagia ceased, the rise in hemoglobin concentration was very slow, in some cases taking eighteen months to return to normal figures. In one of his cases the condition of the blood remained unaltered. Marked improvement, however, usually followed the administration of liver extract and of large amounts of iron. It was also noted that achlorhydria and increased fragility of the red blood cells were features of this syndrome.

During the past two years, eight cases of this syndrome have been studied at the Massachusetts General Hospital, one of which proved fatal following an esophagoscopic accident. The reports of these eight cases, together with the autopsy observations in the fatal case, will now be presented.

#### REPORT OF CASES

CASE 1—S. M. N., the patient, a woman, single, aged 27, after having suffered from dysphagia for three years, sought treatment when this disability had become almost complete. Esophagoscopy revealed a dimple-like opening to the gullet on the right side just below the cricoid. The opening was dilated by means of a plunger, after which a broken web was seen on the right posteriorly. Examination of the blood showed a red cell count of 4,700,000 per cubic millimeter and a hemoglobin concentration of 50 per cent. Achromia, poikilocytosis and anisocytosis of the red blood cells were noted. Pills of ferrous carbonate, U.S.P. (six daily), and varying amounts of whole liver were administered, much improvement taking place, which was maintained for twelve months, then a relapse occurred. Esophagoscopy, performed again two months later, revealed an esophageal opening, 0.5 cm in diameter, and a web situated anterolaterally on the left. The tongue showed a superficial atrophic glossitis, and fissures were present at the angles of the mouth. Neither paresthesia nor any symptoms attributable to anemia were present. The red blood cell count was 4,800,000 and the hemoglobin concentration 50 per cent. The Wassermann test was negative. Gastric analysis after histamine stimulation revealed the presence of free hydrochloric acid and low figures for total acidity. Treatment consisted of esophageal dilation and the administration daily

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<sup>12</sup> Paterson, R. D. Proc Roy Soc Med (Sect Laryng) **24** 1203 1931  
J Laryng & Otol **46** 532, 1931

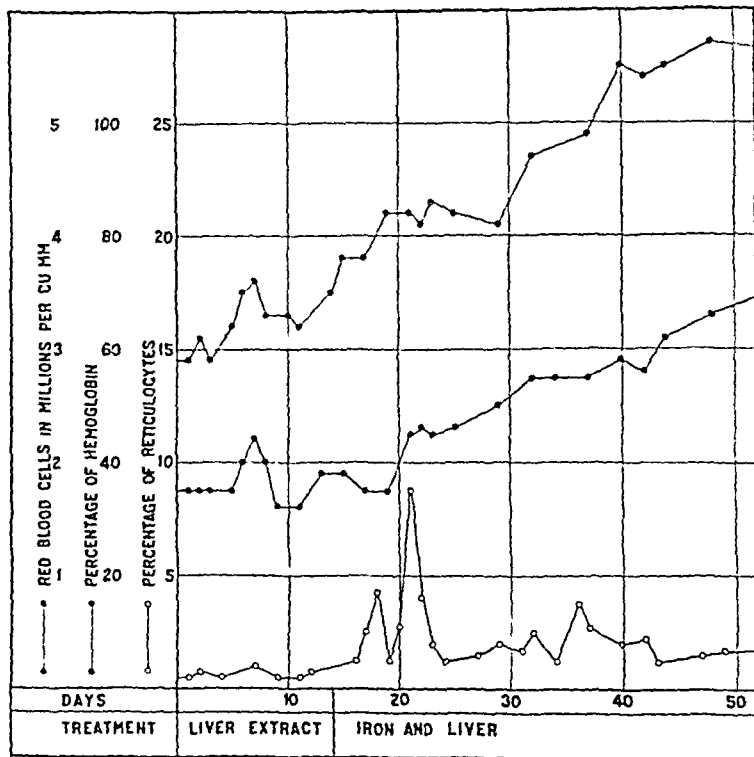
of from 140 to 180 grains (9 to 11.6 Gm) of iron and ammonium citrate and 2 drachms (7.7 Gm) of diluted hydrochloric acid (U S P). With this treatment, although the hemoglobin increased only 10 per cent, there was definite general improvement and the fissures at the angles of the mouth healed promptly. The dysphagia, however, persisted and further instrumentation was found necessary to bring about alleviation of this symptom.

*Comment*—The early age at which the syndrome developed in this patient is noteworthy, as is also the fact that after she had been relieved of the dysphagia by the breaking of a web in the process of dilation, this symptom recurred one year later, owing to the development of another web at a different site.

CASE 2—M M, the patient, a woman, aged 60, single, was admitted to the Massachusetts Eye and Ear Infirmary complaining of difficulty in swallowing of one year's duration, and of loss of weight amounting to 18 pounds (8.1 Kg) in the past seven months. On roentgen examination it was observed that the barium passed to the left through the upper end of the esophagus, the right side being obstructed, and that a web was present immediately below this site. Esophagoscopy revealed a constriction consisting of an anteroposterior band dividing the entrance to the esophagus into two parts. This band was broken, the esophagus then being easily dilated with a large bougie (gauge 36). No examination of the blood was performed at this time. The patient was discharged symptom-free and remained well for four months. Then the dysphagia returned, again necessitating the passing of an esophageal bougie, which resulted in relief from symptoms for a period of four months. In addition to dysphagia, the patient forthwith commenced to suffer from general weakness, dyspnea on exertion, numbness and tingling in the hands and feet, and a sore mouth and tongue. She also noticed that she had become very pale, although some degree of pallor was alleged to have been always present. These symptoms having progressed for a period of three months, the patient was admitted to the Medical Services of the Massachusetts General Hospital in an emaciated condition. The skin was pale with a yellow tinge, the lips were cracked and fissured, and the tongue showed a marked superficial atrophic glossitis, being extremely smooth and glossy. Examination of the blood showed a red cell count of 2,900,000, a hemoglobin concentration of 35 per cent and a white blood cell count of 13,100, with a polymorphonuclear leukocytosis. The red cells were achromic and showed alteration in size and shape, the average diameter being 6.5 microns with a dispersion of 1.4 microns. The blood platelets appeared to be diminished. The icteric index was 3. Serum calcium and phosphorus estimations were, respectively, 8.24 and 4.02 mg per hundred cubic centimeters of blood. The serum protein was 6.9 per cent. The Wassermann and Hinton tests were negative. Gastric analysis revealed a complete absence of free hydrochloric acid after histamine stimulation. The basal metabolic rate was +11 per cent. At roentgen examination a slight narrowing at the entrance to the esophagus was noted. After an esophageal bougie had again been passed, treatment consisted, at first, of the daily administration of liver extract no. 343, N N R, the amount derived from 600 Gm of liver, for a period of eleven days. During this time no significant changes occurred in the numbers of red blood cells and reticulocytes, in the hemoglobin concentration or in the condition of the lips, mouth and tongue, which were extremely sore. However, when 90 grains (5.8 Gm) of iron and ammonium citrate, together with a half-pound (227 Gm) of prepared liver pulp, was administered daily, marked improvement occurred, not only in the condition of the mouth

and tongue but also in the red blood cell count and hemoglobin concentration, which, over a period of thirty-five days, increased to 5,700,000 and 65 per cent, respectively. The reticulocytes responded and reached a peak of 8.6 per cent on the eighth day after liver and iron were first given. The patient was discharged entirely free from symptoms (see chart)

*Comment*—It should be noted that thirty years previously this patient had suffered from a chronic gastric ulcer, for which a gastro-enterostomy had been performed (compare cases reported by Witts<sup>11</sup> and by Davies,<sup>19c</sup> also case 5 in the present series). It is noteworthy that whereas no improvement resulted from the relief of the dysphagia by



The effect of the daily administration of liver extract no. 343 N N R (amount derived from 600 Gm of liver), and of iron and ammonium citrate (3 Gm) together with whole liver (220 Gm) in a case of the "Plummer-Vinson Syndrome" (case 2)

instrumentation and the administration of liver extract, relief of the blood condition and of the soreness of the tongue followed promptly when iron was given in addition to liver

CASE 3—H M F, the patient, a married woman, aged 45, was admitted to the medical services of the Massachusetts General Hospital complaining of difficulty in swallowing of twenty years' duration, and of having been pale for the past thirty years. She did not remember whether the onset of the dysphagia was sudden or gradual, or whether there was any nervous shock or special incident which precipitated her symptoms. The dysphagia was referred to the level of the thyroid and was present at all meals and worse when she felt nervous and when she was watched. Solid food tended to stick, occasionally necessitating regurgita-

tion On one occasion a pea lodged for several days in her throat, preventing her from swallowing even liquids There was no pain, substernal distress, nausea, vomiting, hematemesis, diarrhea or tarry or bloody stools Her diet was thus limited, consisting chiefly of fruit juices, beverages, milk and milk products, eggs and carefully prepared cereals and vegetables Eight years previously, she noticed that her skin was yellow for a period of one year Soreness of the mouth and tongue, worse at night and while eating, was first experienced three years previously There were no neurologic symptoms, such as numbness and tingling of the extremities or difficulty in walking During the past twenty years, she had lost 33 pounds (14.9 Kg) She had been pregnant six times

On examination, the tongue, which appeared small and atrophied, showed a marked superficial atrophic glossitis, being smooth and shiny The right side was especially red and inflamed On the under surface there were small grayish areas, not raised or hard, but somewhat tender The patient was unable to protrude the tongue far because, on attempting this, severe pain was experienced Moreover, it appeared that the tongue was somewhat fixed The buccal mucous membrane showed shiny red areas, on which was superimposed a leukoplakia-like condition The gums were spongy and the lips dry, with fissures at the angles of the mouth Esophageal examination revealed a stricture at the entrance to the esophagus, the lumen at this site being one-third its normal size On roentgen examination, there was an irregular constriction in the upper end of the esophagus, beginning about 1 inch (2.5 cm) below the entrance and extending for a distance of  $1\frac{1}{2}$  inches (3.8 cm), reducing the lumen to one-third its normal diameter

The red blood cells numbered 4,200,000, and showed moderate achromia and alteration in size and shape The average diameter was 7.4 microns, with a dispersion of 1.2 microns The hemoglobin concentration was 60 per cent The total and differential white blood cell counts were normal Apart from the presence of a few blood cells in the urine for a period of a few days, the urine was essentially normal The Wassermann and Hinton tests were negative The basal metabolic rate was +3 per cent A tube could not be passed for the purpose of a gastric analysis Microscopic examination of a smear taken from the mouth did not reveal Vincent's organisms

Treatment consisted of the daily oral administration of liver extract for a period of one month (no. 343, the amount derived from 600 Gm of liver, replaced later by 2 ounces [59.1 Gm] of E 49 Valentine) No improvement in the buccopharyngeal or the blood condition having taken place from the use of liver extract, the esophageal introitus was dilated on two occasions This procedure caused so much pain that the patient was unable to eat or drink for several days and lost 7 pounds (3.1 Kg) Improvement in swallowing occurred later, however, and a diet of high caloric content was instituted No change was noted in the blood, and the patient was discharged During the next few months, although the administration of 60 grains (3.8 Gm) daily of iron and ammonium citrate together with liberal amounts of liver extract brought about a slight increase in the number of red blood cells and in the percentage of hemoglobin, no improvement was noted in the buccal lesions A biopsy was therefore performed on the scarlike tissue of the right side of the tongue and of the anterior pillar of the fauces This showed a squamous cell carcinoma This observation necessitated the resection of the right anterior pillar of the fauces and a portion of the base of the tongue and of the buccal mucosa, in addition to a block dissection of the glands of the neck A recurrence occurred later, for which roentgenotherapy was employed

*Comment*—The importance of this case lies in the continued severity of the lesions of the tongue, mouth and pharynx in spite of treatment

with liver and iron and by instrumentation, and the subsequent development of malignant disease at these sites. It is noteworthy that neither the administration of liver extract nor relief of the dysphagia brought about improvement in the condition of the blood, whereas, when iron was given, a slight, though definite, increase took place in the number of red blood cells and in the hemoglobin concentration.

CASE 4—B. H. F., the patient, a married woman, aged 46, was admitted to the Massachusetts General Hospital complaining of difficulty in swallowing, dryness of the mouth and throat, loss of strength, shortness of breath and palpitation. These symptoms had existed for four years. The dysphagia was referred to the level of the thyroid and was more severe when the patient swallowed solids than when she swallowed liquids. The tongue was not sore, nor were paresthesias present.

On examination, the tongue showed atrophy of the mucous membrane, which was smooth and shiny. Cracks and fissures were present at the corners of the mouth, and the patient was edentulous. Roentgen examination revealed a constriction at the entrance to the esophagus. The red cell count was 3,800,000, the hemoglobin concentration 55 per cent and reticulocytes 1 per cent. The red blood cells showed achromia, rare polychromatophilia and distinct alteration in size and shape. The total and differential white blood cell counts were considered normal. The icteric index was 5. The Hinton blood test was negative. Gastric analysis, after histamine stimulation, revealed a complete absence of free hydrochloric acid and a low content of combined acid. The urine was not abnormal. Treatment, consisting of the administration of iron and ammonium citrate (90 grains daily), a high caloric diet and dilation of the esophageal stricture, brought about distinct improvement both in the blood condition and in ability to swallow.

*Comment*—Since the dysphagia and the symptoms attributable to anemia appeared simultaneously, and as it takes time for enough anemia to develop to cause palpitation and dyspnea, it is almost certain that some degree of anemia had been present before the onset of the difficulty in swallowing.

CASE 5—K. H. G., the patient, a married woman, aged 53, was admitted to the Massachusetts General Hospital complaining of general muscular weakness, palpitation, dizziness, nausea, vomiting and a yellowish pallor of the skin, all of four years' duration, although more marked during the past year. During the past four months sores had frequently appeared on her lips. Two years before the onset of these symptoms, a laparotomy had been performed on account of marked abdominal pain with nausea and vomiting. A gastric ulcer was found, for which a sleeve resection of the stomach and a posterior gastro-enterostomy were performed, resulting in much relief. It should be noted that there had been no complaint of difficulty in swallowing.

Studies of the blood revealed a red cell count of 2,400,000 and a hemoglobin concentration of 40 per cent. A considerable degree of achromia was present, with marked poikilocytosis and moderate anisocytosis. Although macrocytes were present, they were not well filled with hemoglobin. Some degree of polychromasia was noted. The total and differential white blood cell counts were normal, and the blood platelets were diminished in number. Examination of the urine yielded negative results. The gastric contents contained no free hydrochloric acid and small amounts of combined acid. The spleen and liver were palpable. The tongue



was smooth and devoid of papillae. In the course of a roentgen examination of the gastro-intestinal tract, it was observed that the esophagus presented no abnormality. Treatment consisted of transfusion of blood and the administration of a diet of high caloric content.

Seven years later, this patient returned to the hospital complaining of occasional attacks of vomiting and diarrhea, and of difficulty in swallowing of three years' duration, the obstruction being referred to the level of the thyroid and encountered only with solid food. The tongue was small and atrophic with a smooth and shiny mucous membrane, totally devoid of papillae. Fissures were present at the corners of the mouth. The spleen was palpable, but the liver was not enlarged. Examination of the central nervous system revealed nothing abnormal. Anemia was still present, the red blood cell count being 3,500,000 and the hemoglobin concentration 40 per cent. There was marked achromia with much alteration in the size and shape of the red blood cells. Treatment, consisting of the administration of 90 grains daily of iron and ammonium citrate, was instituted. Unfortunately, however, up to the time of writing, no data were available concerning the effects of this therapy.

*Comment*—This case is of especial importance, first, in that two years after a partial gastrectomy with gastro-enterostomy, there developed a hypochromic anemia with atrophy of the mucous membrane of the tongue, and second, in that the latter features antedated the dysphagia by four years. It is obvious, therefore, that in this case the anemia was not the result of a restricted diet dependent on the difficulty in swallowing.

CASE 6—A F M, the patient, a woman, aged 58, was admitted complaining of numbness and tingling of the fingers for two years and of the toes for six months. Shortness of breath on exertion, dizziness and general weakness had been features for several months, and weakness and stiffness of the legs for two months. Indigestion, with occasional attacks of nausea, vomiting and diarrhea, had been present for many years. The patient stated that she had had no meat for fifteen years, having lived chiefly on eggs, bread and vegetables. The tongue had never been sore. Mild difficulty in swallowing, referred to the level of the thyroid and encountered only with solids, had been developing gradually for several months. The mucous membrane of the tongue showed a moderate degree of atrophy, being smooth and shiny chiefly along the edges. Roentgen examination revealed a constriction at the upper end of the esophagus. No abnormal physical signs were revealed on examination of the nervous system, nor was the cerebrospinal fluid abnormal. A tube could not be passed for the purpose of a gastric analysis. Studies of the blood revealed a red blood cell count of 4,500,000 and a hemoglobin concentration of 60 per cent. The red blood cells were somewhat achromic and varied in size and shape. The total and differential white blood cell counts were normal. Esophageal dilation brought about much improvement in swallowing.

*Comment*—This case is of interest in that intense paresthesia of the extremities was complained of, and this in spite of the mild degree of anemia present. Although no organic neurologic abnormalities were found on examination, definite difficulty in walking was a feature, this may well have been due to the severe numbness and tingling.

CASE 7—A O B, the patient, a married woman, aged 61, was admitted complaining of difficulty in swallowing solid food for seven years. The diet had become progressively limited, and had consisted for about two years chiefly of milk, cream, eggs and meat and fish broths. For the past five years she had experienced gradually increasing weakness, attacks of dizziness, dyspnea, palpitation and swelling of the ankles. Constipation had alternated with attacks of diarrhea for the past two years. Soreness and tenderness of the lips, tongue and throat, cracking of the angles of the mouth and numbness and tingling of the fingers and toes on exposure to cold had been features during the past twelve months. There had been no nausea or vomiting, and the appetite had remained good. She had had six children, two of whom died within a few months of birth, and, in addition, two miscarriages.

On examination, the patient appeared pale, thin and undernourished with a yellow tint to the skin. The nails were spoon-shaped, with longitudinal splitting and striations. Cataracts were present in both eyes. There were fissures at the angles of the mouth, the tongue was small and atrophic, and the mucous membrane smooth, tender and devoid of papillae. Edema of the feet and lower part of the legs was present. The spleen was not palpable, but the liver was enlarged, the lower edge being palpable 3 cm below the costal margin. Studies of the blood showed a marked anemia, with a red cell count of 1,800,000 and a hemoglobin concentration of 15 per cent. There were marked achromia and marked alteration in size and shape of the red blood cells. Macrocytosis was not a feature. A leukopenia was present, the white blood cell count being 3,000. The differential count, however, was not abnormal. The serum protein was 6.3 per cent, and the non-protein nitrogen content 23 mg per hundred cubic centimeters of blood. The urine contained a trace of albumin and numerous pus cells. The Wassermann reaction was negative and the blood pressure 142 systolic and 70 diastolic. Gastric analysis, after histamine stimulation, revealed the absence of free hydrochloric acid. Treatment consisted of the intramuscular administration of 900 mg of ferric citrate over a period of three days. The percentage of reticulocytes rose to 7.6 on the sixth day, and after two weeks the number of red blood cells had increased to 2,500,000 and the hemoglobin concentration to 23 per cent. The further intramuscular administration of 1,600 mg of iron citrate over a period of four days evoked a second reticulocyte rise with a peak of 5.6 per cent on the sixth day, the red blood cell count and hemoglobin concentration continued to increase, reaching 3,000,000 and 35 per cent, respectively, on the twentieth day after the second course of iron. Marked improvement in the lesions of the lips and tongue was noted. Regeneration of papillae on the tongue, previously completely denuded, was a striking feature. Further, although no instrumentation had been resorted to, the difficulty in swallowing was somewhat alleviated.

*Comment*—The unusual severity of the anemia and the well marked spoon-shaped deformity with longitudinal splitting of the nails are notable features in this case. The fact that regeneration of lingual papillae occurred with iron therapy is of importance, in that it may throw some light on the underlying nature of this syndrome.

CASE 8—E M F, the patient, a woman, aged 48, single, was admitted complaining of occasional nausea and vomiting, of a feeling of fulness after eating and pressure in the chest for the past ten years, and of having passed bright blood by rectum at intervals for six years. About four years before admission she commenced to have difficulty in swallowing solid food, numbness and tingling of the

fingers and toes, slight unsteadiness on walking, dyspnea on exertion, palpitation, dizziness and swelling of the ankles. She had lost 15 pounds (6.8 Kg) in the past two years. Although her tongue had never been sore, she occasionally suffered from painful "cankers" in the mouth. Her diet, necessarily limited, had included little meat or vegetables. She did not remember the duration of her pallor.

On examination, the patient appeared pale, undernourished and poorly developed, with a slight icteric tinge of the skin and conjunctivae. There were fissures and scars at the angles of her mouth. The tongue appeared small and shriveled, and the mucous membrane presented a pale, smooth, somewhat glazed appearance, being devoid of papillae. The buccal mucosa was similarly pale and smooth. The patient was edentulous. The spleen and liver were not palpable. Examination of the blood revealed a moderate degree of hypochromic anemia. The red blood cells numbered 3,500,000, of which 0.8 per cent were reticulocytes. The hemoglobin concentration was 30 per cent, and the total and differential white blood cell counts were normal. The red blood cells appeared achromic, with much variation in size and shape. Examination of the urine and the Hinton blood test yielded negative results. The stools contained occult blood. Although the basal metabolic rate was -33 per cent, no hypothyroid symptoms were present. Fluoroscopic examination of the esophagus revealed an obstruction at the level between the sixth and seventh cervical vertebrae, this was considered to be due to a constricting band or web. Esophagoscopy (performed in the Nose, Throat and Ear Department), revealed a stricture immediately below the entrance to the esophagus. The constriction was dilated by means of bougies, the last of which met with some resistance, and slight bleeding was noted at the tip of the bougie after removal.

The day following endoscopy, the patient complained of pain between the shoulders, and, on examination, subcutaneous emphysema was detected above the clavicle. Two days later, roentgen examination of the chest revealed fluid at the base of both lungs, consolidation in the right lung and air in the mediastinum. Fever developed and the temperature was 101.6 F. The pulse rate had increased to 100 per minute, and a polymorphonuclear leukocytosis with 29,000 white blood cells per cubic millimeter was present. On the fourth day there was much respiratory distress, and a physical examination pointed to the presence of much fluid in the right side of the chest. The following day, the respiratory rate having increased to 60 and the pulse rate to 135 per minute, with much distress, paracentesis of the right side of the chest was performed, and 1,400 cc of hazy fluid was removed. This contained numerous polymorphonuclear cells and gram-positive cocci in short chains. The patient died the following day.

*Autopsy*—The autopsy was performed by Dr. John I. Bradley two and one-half hours post mortem. The body was small, poorly developed and undernourished. Slight pitting edema of the lower extremities was present. Large hemorrhoidal masses were noted. There was only a small amount of subcutaneous fat. No gross pathologic abnormalities were noted in the pericardial or peritoneal cavities, heart, gastro-intestinal tract, bile ducts, spleen, pancreas or its ducts, suprarenals, kidneys, bladder or thyroid gland. In the liver, which weighed 1,900 Gm, two small circumscribed, rounded, yellowish nodules were noted, these resembled the liver tissue as seen in the nodular areas of regeneration. The right pleural cavity contained approximately 800 cc of thin, turbid, yellowish, purulent fluid. The pleural surfaces were coated with a thin layer of fibrin. An irregular, ragged, oval perforation was present in the mediastinal pleura near its center. Thick, purulent, yellowish fluid could be expressed through this perforation. The left pleural cavity showed no abnormality, except a few slight adhesions in the

lower lateral and posterior portions. The right lung was smaller than the left, and much firmer and less crepitant than normal, having a doughy consistency. No definitely consolidated areas were palpable. The cut surface was homogeneous throughout and light pinkish-gray, and exuded considerable thin frothy fluid. A few small, slightly elevated grayish patches were present in the central portion of the lower lobe. The left lung was normal except for moderate edema and congestion. The aorta and pulmonary artery showed slight atheromatous deposits. The ovaries were normal in size, one containing a single follicular cyst and the other a small fibromatous mass. The uterus was normal except for several small intramural fibroids.

*Tongue*—Along both sides and over most of the superior surface of the tongue the mucosa was smooth, glistening and whitish in appearance. The whole organ was thin and atrophic. The papillae were absent, except at the tip and in the central portion of the superior surface.

*Esophagus*—Extending along the lateral and posterior surfaces of the esophagus from the level of the larynx to the diaphragm, there was a well defined, narrow, irregular space, measuring roughly 3 cm in width and 15 cm in depth, which contained thick, yellowish, purulent fluid. There was no gross defect in the wall of the esophagus. On probing the superior esophageal orifice with the little finger a definite constriction was noted, although no obstructing band was seen.

On opening the esophagus there was seen on the anterior and left lateral surface of the esophageal wall just below the introitus and lying over the left posterior portion of the larynx, just below the left pyriform sinus, a relatively large, irregularly triangular area, roughly 2.5 by 1.5 by 2.5 cm in area, which appeared sharply demarcated from the adjacent normal mucosa. The surface of this area was smooth and yellowish white, but less smooth and glistening than the adjacent mucosa.

At the lateral and posterior margins of the triangular area described, there was a small free fold of mucosa, which could be brought over to the region of the upper right central apex of the triangular area. When this was done, the apparent defect in the mucous membrane was closed. The appearance suggested that this was the relationship before instrumentation and that the esophageal obstruction had been due to a mucosal band, narrowing the lumen of the esophagus in the first portion along the left side.

At the inferior apex of the triangle there was a definite fold of mucous membrane extending across from the anterior central to the left lateral portion of the lumen. A blunt probe inserted in the pocket anterior to this fold passed easily through the esophageal wall into the superior portion of the para-esophageal mediastinal abscess cavity. The tissues around the outer margins of this defect in the esophageal wall appeared irregularly lacerated, but did not show much gross inflammatory reaction. The remainder of the esophagus showed no definite abnormality, except a slightly elevated, finely granular, whitish patch about 1.5 by 1 cm in area and 3 mm in height in the central portion of the esophageal interior.

*Bacteriologic Examination*—The blood of the right and left sides of the heart on culture showed a growth of the hemolytic streptococcus. Gram-positive diplococci in chains were noted in the right pleural cavity and mediastinum.

*Microscopic Examination*—The heart showed slight perivascular fibrosis. On the pleural surface of the lung there was a thick dense layer of fibrin with polymorphonuclear cells, both of which were also present in the subpleural lymphatics and in many of the alveoli. The liver showed slight central congestion. The liver cells in the centers of the lobules were acidophilic and contained considerable brown pigment. A few small focal areas of necrosis of liver cells and polymorphonuclear

infiltration were seen. There was no evidence of syphilis. The pancreas showed a slight degree of interstitial fibrosis. In the spleen, the pulp contained numerous large immature unrecognized cells, which showed occasional mitotic figures. Numerous normoblasts but no megakaryocytes were seen. The malpighian corpuscles were small and inactive, and the arterioles showed moderate hyaline changes. The kidneys showed no abnormalities except a small amount of hyaline material in some arterioles. The suprarenal glands showed no significant abnormality. In the aorta, moderate fibrous intimal thickening and atheromatous change were noted. The thyroid gland showed a slight diffuse increase in the stroma producing a definite separation of the acini. In the mediastinal tissue, edema, a fibrin deposit and an infiltration with mononuclear cells and polymorphonuclear leukocytes were noted. The bone marrow showed a marked diffuse hyperplasia, with both erythropoiesis and granulopoiesis well represented. There were numerous normoblasts scattered diffusely throughout, without regular grouping. Numerous myelocytes, particularly eosinophilic, were present, and megakaryocytes in more than normal proportions.

*Tongue*—The epithelium showed marked keratinization extending even into the deeper layers, and in some areas was markedly thinned. Some degree of desquamation was also present. There was a slight lymphocytic infiltration beneath the mucosa. Large deposits of fat were present between the muscle fibers, and there appeared to be a considerable diminution in the amount of muscle tissue present. Fat granules were noted in the muscle fibers and were aggregated chiefly at the poles of the sarcolemma nuclei. In many of the muscle fibers an increase in the number of sarcolemma nuclei was observed, in some instances being associated with an apparent disappearance of the muscle fibers and an interruption of the continuity of the muscle bundle, which was represented only by lines of sarcolemma nuclei. A few places showed small irregular deeply acidophilic areas suggestive of Zenker's degeneration.

*Esophagus*—Sections of the proximal, central and distal portions of the esophagus showed similar changes throughout. The epithelium presented (1) a basal layer and (2) extensive desquamation, of varying degrees, of the hyperkeratinized superficial epithelium. The latter resulted in a marked irregular thinning of the epithelium, leaving at times only a single layer of cells. Where this was the case the cells were long and slender, and projected out radially from the esophageal wall in a brush border, giving the surface a very irregular outline. In other sections the epithelium was composed of rather large cells appearing somewhat immature and containing large vesicular nuclei with occasional mitotic figures, giving an appearance somewhat similar to that of leukoplakia.

The submucosa, mainly in the areas where the epithelium was thinned, showed a moderate degree of infiltration with mononucleated cells, chiefly lymphocytes and plasma cells.

The striated muscle in the proximal portion showed a number of homogeneous, deeply acidophilic hyaline areas suggestive of Zenker's degeneration. The smooth muscle throughout presented marked degenerative changes consisting of shrinkage, loss of normal outline and the presence of numerous small hyaline masses. The latter changes were regarded as being probably postmortem artefacts.

Sections from the very proximal end of the esophagus in the region of the triangular defect in the mucosa showed an area in which the epithelium was missing and the surface covered by a dense fibrin layer. There was marked acute inflammatory infiltration in the adjacent tissues. The striated muscle showed extensive changes consisting of disappearance of the normal cross-striations with longitudinal splitting of the fibers and the presence of aggregations of large numbers of nuclei.

within the sarcolemma. In some places, collections of nuclei were noted, consisting of as many as from twenty to thirty in apposition.

No abnormalities were discerned in the intermuscular nerve plexus of Auerbach, which was readily identified throughout the whole esophagus, except at the pharyngo-esophageal junction.

The liver was assayed for its vitamin A content by the antimony trichloride method of Carr and Price,<sup>13</sup> using the Rosenheim-Schuster modification of the Lovibond tintometer, and expressing the results in "blue units" per gram of tissue per "centimeter cube" according to the method of Moore.<sup>14</sup> It is of interest to note that small, though significant, amounts of vitamin A were present (69 blue units per gram of liver).

*Comment*—It appears that the filiform bougie became caught in a fold of mucous membrane, which it readily perforated, and then passed through the esophageal wall into the mediastinal space. The danger of passing an unguided filiform bougie into the esophagus is thus clearly demonstrated. From the gross findings, it is evident that a real obstruction, brought about by raised folds of mucous membrane, was present.

The mucosa and muscle of the tongue and esophagus showed definite histologic abnormalities, consisting chiefly of hyperkeratinization of the epithelium with areas of desquamation and of degenerative atrophic changes in the underlying muscle. Although there was a moderate degree of infiltration of the submucosa with lymphocytic-like cells, on the whole the condition did not appear to be inflammatory. The possibility that the hyperkeratinization of the epithelium may have been dependent on a deficiency of vitamin A is offset by the detection of significant amounts of this substance in the liver. The presence of areas of mucous membrane simulating leukoplakia and containing immature cells exhibiting mitoses, is of interest, in view of the tendency of malignant disease to develop (see case 3).

#### COMMENT

A discussion of the significance of the clinical and pathologic aspects of this syndrome is presented here.

In spite of the frequent occurrence of webs, bands or raised folds of mucous membrane obstructing the esophageal entrance, the majority of writers have tended to regard the esophageal obstruction as being due to spasm, while Hurst<sup>15</sup> has held the view that the nature of the obstruction was that of failure of the pharyngo-esophageal sphincter to relax (i. e., achalasia), rather than that of spasm.

Various reasons have been suggested to explain the alleged spasm or failure to relax of the pharyngo-esophageal sphincter. Vinson,<sup>3</sup>

13 Carr, F. H., and Price, E. A. *Biochem J* **20** 497, 1926.

14 Moore, T. *Biochem J* **23**.1267, 1929.

15 Hurst, A. F. *Brit M J* **1** 375, 1928.

Moersch and Connel<sup>5</sup> and Ryle<sup>7</sup> regarded the spasm as functional or hysterical in nature. However, in view of the well marked gross and microscopic lesions found in the pharyngo-esophageal region in my case, it seems unnecessary that hysteria be considered in the etiology of this disease. Moreover, other hysterical phenomena are not as a rule present, nor can the dysphagia be cured by purely functional means, although certain physicians have stressed the value of reassurance and suggestion in addition to the usual methods of treatment.

Kelly<sup>1</sup> mentioned the possibility of the presence of inflammatory involvement of the nerve supply in the pharyngo-esophageal region, which he held would tend to cause hyperesthesia of the sensory side or stimulation of the motor side, thus leading to spasm. Similarly, Huist<sup>15</sup> suggested that there may be involvement of Auerbach's plexus by a direct spread of the inflammation from the mucous membrane to the deep lying plexus, thereby interfering with the normal neuromuscular mechanism, in a way similar to that found in achalasia of the cardia.<sup>16</sup> Cameron<sup>17</sup> was also of the opinion that the local nerve tissue may be involved, but pointed out that, since there is no intermuscular plexus within 2 cm. of this region, the nerve tissue involved must be that of the nerve terminals in the epithelium. However, since there was no evidence of neurologic involvement in the pharyngeal or esophageal tissues in the case at autopsy, this hypothesis does not appear to be substantiated. Moreover, the histologic picture in this case was quite unlike that which I<sup>16d</sup> have noted in several cases of cardiospasm, in which the involvement of the nerve tissue was unmistakable and widespread, thereby confirming the observations of Rake<sup>16b</sup> and of Cameron<sup>16c</sup> concerning the histopathologic changes found in cardiospasm. Moreover, it seems superfluous to predicate spasm or achalasia as an explanation of the difficulty in swallowing in the so-called Plummer-Vinson syndrome, when a definite cause for obstruction, namely, webs, bands or raised folds of mucous membrane, is so often apparent.

The conception of the nature of the obstruction held by Hill<sup>18</sup> is of interest. This writer pointed out that there is no true sphincter at the upper end of the esophagus, there being no aggregation of circular fibers. What he considered occurs in this condition is not an active contraction, obstructive or otherwise, but a passive or feebly active condition of the musculature concerned in the pharyngeal part of the

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16 (a) Rake, G. W. *Guy's Hosp. Rep.* **76** 145, 1926, (b) *ibid* **77** 141, 1927 (c) Cameron, M. J. *Laryng. & Otol.* **43** 219, 1928 (d) Suzman, M. M. Unpublished data (paper read before the Newcastle-upon-Tyne Pathological Club, Feb. 21, 1929)

17 Cameron, M. *Brit. M. J.* **1** 521, 1928

18 Hill, W. *Brit. M. J.* **1** 467, 1928

act of deglutition. In other words, the interference with swallowing is of the nature of a muscular paresis together with reduced sensibility of the mucosa, rather than hyperesthesia and increased reflex contraction. Swallowing is impeded owing to feeble effort and the fact that the pharyngo-esophageal junction is not well opened up on account of impaired reflex stimulus. Hill is of the opinion that the atrophic lesion in the lower part of the pharynx in these feeble anemic patients is in many respects similar to that observed in patients with chronic nasal catarrh, whose palate is thinned, shrunken and almost immobile and who show atrophy of the glands, mucosa and muscles. This conception of the nature of the pharyngo-esophageal condition is of interest in view of the fact that, in the case coming to autopsy, atrophic changes were noted not only in the mucosa but also in the muscle tissue of this region.

The view of Evans,<sup>10</sup> that the underlying cause of the lesions of the mouth, tongue, pharynx and esophagus is syphilis, is not substantiated by the histologic observations, either at these sites or in the tissues of the other organs. Moreover, the histologic evidence that these lesions are truly inflammatory is scanty, since the chief findings were those of hyperkeratinization of the epithelium, with areas of desquamation, and an atrophic degeneration of the underlying muscle tissue. This is of importance since these lesions have usually been regarded by most writers as inflammatory and are referred to as "glossitis" and "esophagitis." It will be recalled that Hurst<sup>6</sup> and Ryle<sup>7</sup> considered the condition of the tongue as a streptococcal glossitis.

The relationship between the anemia and the dysphagia has always been a subject of contention. It has usually been held that the dysphagia is the primary disease, and that the anemia is secondary, developing as a result of the consequent unbalanced and restricted diet. To support this view, it has been put forward that the anemia usually develops in patients who have suffered from dysphagia for years. Witts,<sup>11</sup> however, has remarked on the fallacy of placing too much reliance on the sequence of events, pointing out that, whereas dysphagia is usually an alarming symptom, anemia and glossitis may easily pass unnoticed. Moreover, that the anemia may precede the onset of the dysphagia, even by many years, has been reported by several writers,<sup>19</sup> and was obvious in my case 5.

Another reason usually cited as evidence of the dependence of the anemia on the dysphagia is that, following the relief of the latter by means of instrumentation, improvement in the condition of the blood

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19 (a) Moersch and Conner<sup>5</sup> (b) Hurst<sup>6</sup> (c) Cameron<sup>9</sup> (d) Witts<sup>11</sup>  
(e) Davies, D. T. *Lancet* 2 385, 1931



is said usually to take place. It should be borne in mind, however, that, in addition to the passage of bougies, treatment usually consisted also of the administration of iron and arsenic. In this connection, the observations of Johnson<sup>20</sup> are of importance. This investigator pointed out that after the passage of bougies, although dysphagia ceased, the rise in the hemoglobin concentration, if it occurred at all, was extremely slow, taking in some cases a period of eighteen months to return to normal figures, whereas he obtained improvement in the condition of the blood after the administration of liver extract and of large doses of iron. It seems, therefore, from these considerations, that the contention that the development of anemia is dependent on the dysphagia cannot be upheld.

That the esophageal lesions and the consequent difficulty in swallowing are probably the result of an extension to the pharyngo-esophageal region of the lesions of the mouth and tongue is demonstrated by the fact that the latter may exist for a considerable time before the onset of the dysphagia,<sup>21</sup> and that they are usually present when the dysphagia is first noticed.<sup>22</sup> Further evidence to support this view is the apparent histologic identity of the lesions of the tongue and of the pharyngo-esophageal region (case 8).

Except for the dysphagia, all the manifestations of this syndrome, including the response to iron therapy, are indistinguishable from those of idiopathic hypochromic anemia,<sup>23</sup> also described under various other terms, such as achylic chloranemia,<sup>24</sup> idiopathic secondary anemia,<sup>25</sup> chronic hypochromic anemia<sup>26</sup> and simple achlorhydric anemia.<sup>27</sup>

The dysphagia, it seems, is merely a complication or concomitant manifestation of this already well recognized form of anemia, and there does not appear to be sufficient reason to regard this so-called "Plummer-Vinson syndrome" as a separate clinical entity. From an etiologic standpoint, therefore, this syndrome may be considered simply one that may arise in "idiopathic hypochromic anemia."

Since the administration of large amounts of iron almost invariably relieves the anemia and usually alleviates the lesions of the tongue and

20 Johnson, R. S. *Proc Roy Soc Med (Sect Laryng)* **24** 1206, 1931.

21 Davies<sup>19e</sup> Case 5 of present series.

22 Paterson<sup>12</sup> Davies<sup>19e</sup>

23 Mills, E. S. *Canad M A J* **22** 175, 1930. Minot, G. R., and Health, C. W. *Am J M Sc* **183** 110, 1932.

24 Kaznelson, P., Reimann, F., and Weiner, W. *Klin Wchnschr* **8** 1071, 1929.

25 Watkins, C. H. *A Classification of Chronic Idiopathic Secondary Anemia*, *J A M A* **93** 1365 (Nov 2) 1929.

26 Altschuller, G. *Acta med Scandinav* **70** 119, 1929.

27 (a) Davies<sup>19e</sup> (b) Witts, L. J. *Guy's Hosp Rep* **80** 253, 1930. (c) Davies, D. T. *Quart J Med* **24** 447, 1931.

mouth, a virtual deficiency of this metal may play some part in the etiology of this disease, be it a lack of supply, a failure of absorption or an inability to utilize the metal. In view of the recent work concerning the rôle of the stomach in the etiology of anemia,<sup>28</sup> it is not improbable that the underlying cause of idiopathic hypochromic anemia and thus of the syndrome, glossitis, dysphagia and anemia, is in the nature of a deficiency dependent on a gastric abnormality.

#### SUMMARY

1 In addition to a short review of the literature, the reports of eight cases of the syndrome of anemia, glossitis and dysphagia (the so-called "Plummer-Vinson" syndrome) are presented, together with the observations at autopsy in one instance.

2 Throughout the tongue, hypopharynx and esophagus, microscopic examination disclosed a condition of hyperkeratinization of the epithelium with areas of desquamation and an atrophic degeneration of the underlying muscle tissue. The intermuscular nerve plexus (Auerbach) revealed no abnormality. The condition did not appear to be inflammatory.

3 A discussion of the etiology of this syndrome and of its relationship to "idiopathic hypochromic anemia" is presented.

Dr James H. Means granted permission to use the cases in the medical services and outpatient departments of the Massachusetts General Hospital for this study.

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28 Davies (footnotes 19<sup>e</sup> and 27<sup>e</sup>) Mettier, S. R., and Minot, G. R. *Am J M Sc* **181** 25, 1931. Castle, W. B. *ibid* **178** 748, 1929. Castle, W. B., and Townsend, W. C. *ibid* **178** 164, 1929. Castle, W. B., Townsend, W. C., and Heath, C. W. *ibid* **180** 305, 1930. Castle, W. B., Heath, C. W., and Strauss, M. B. *ibid* **182** 741, 1931.

# BLOOD CHOLESTEROL IN THYROID DISEASE

## I ANALYSIS OF FINDINGS IN TOXIC AND IN NONTOXIC GOITER BEFORE TREATMENT

LEWIS M HURXTHAL, M D

BOSTON

In December, 1930, Mason, Hunt and I<sup>1</sup> published observations on the blood cholesterol in hyperthyroidism and hypothyroidism. The results of forty-seven determinations of the blood cholesterol in patients with toxic goiter were reported, and it was definitely shown that low values were found in severe cases, although there appeared to be no individual reciprocal relationship between the elevation of the basal metabolic rate and the lowering of the blood cholesterol. The present study was begun on a larger group of patients to determine whether our impression that the degree of clinical toxicity is reflected more accurately in the lowering of the blood cholesterol than by the basal metabolic rate is correct. Furthermore, the behavior of the blood cholesterol as the result of the various therapeutic procedures warranted further study.

### METHOD OF STUDY

The cases studied were unselected, specimens of the blood having been taken as a routine in all cases of goiter. Thus the series is practically consecutive. In all of the cases in this group a metabolism test was made on the morning after admission to the hospital (unless the patient was too ill). Following this procedure, specimens of the blood were taken before the patient was given breakfast. While the blood cholesterol is not appreciably affected if the determination is made shortly after a meal, it was considered desirable to obtain the blood under uniform conditions. With rare exceptions, all specimens of blood were taken in this manner.

Analysis of the plasma was made by the method of Bloor, Pelkan and Allen<sup>2</sup> under the supervision of Miss Hazel M. Hunt, director of the laboratories at the New England Deaconess Hospital. Duplicate

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From the Medical Department of the Lahey Clinic and the Chemical Laboratories of the New England Deaconess Hospital.

1 Mason, R. L., Hunt, H. M., and Hurxthal, L. M. Blood Cholesterol Values in Hyperthyroidism and Hypothyroidism. Their Significance, *New England J. Med.* **203** 1273 (Dec. 25) 1930.

2 Bloor, W. R., Pelkan, K. F., and Allen, D. M. *J. Biol. Chem.* **52** 191 (May) 1922.

analyses were made on all specimens. With the technic employed in this laboratory, the probable error does not exceed 5 per cent (over 1,700 separate specimens of blood were analyzed in this study alone). Hemolysis was encountered occasionally, but this does not appear to affect the result. All specimens were separated from the plasma on the same day, and were precipitated and analyzed when time permitted.

#### EXOPHTHALMIC GOITER

*Effect of Previous Administration of Iodine*—The blood cholesterol was determined in two hundred and eighty-three patients with exophthalmic goiter on their admission to the hospital. These cases were divided into three groups as follows: (1) those in which some form of iodine had apparently been given before the patients came under observation, (2) those in which it was stated that the patients had received

TABLE 1—*Exophthalmic Goiter. Average Cholesterol on Admission to Hospital in 283 Cases Grouped According to the History of Taking Iodine Previously\**

Groups	Cholesterol, Mg per 100 Cc	Average Basal Metabolic Rate, per Cent	Average Pulse Rate	Average Weight in Pounds	Average Percentage Deviation from Normal Weight	Number of Cases
Iodine taken before admission	134	+42	103	126	— 8	129
Indefinite history regarding iodine	133	+47	110	125	— 9	30
No history of having taken iodine	127	+48	109	118	—11	124
Total of three groups						283

\* Fractions are omitted, the nearest integral being chosen.

no form of iodine, and (3) those in which the question of the administration of iodine could not be answered. The average of these findings is shown in table 1. (Tables showing individual analyses will be published in a separate article on the effect of treatment.) It is interesting to note that the average cholesterol value in each group differs in about the same magnitude as the metabolism, pulse rate and weight.

*The Numerical Distribution of Cholesterol Values in Exophthalmic Goiter*—The lowest value found for those patients who gave no history of receiving iodine before coming under our care was 53 mg per hundred cubic centimeters. The highest figure found was 245 mg. The smoothed frequency curves are seen in chart 1. The shift of the curve to the left of that produced by the values found in nontoxic goiter is evident.

*Comparison of Average Cholesterol Values with Average Deviation from Normal Weight and History of Weight Lost*—Those cases in which there was no history of the patient's having taken iodine were

used for this analysis. This tabulation is to be seen in tables 2 and 3. In a general way, the average cholesterol values decrease slightly in the groups which lost the greatest weight, but the difference is not so striking as will be found in comparison of the average observed values in severe hyperthyroidism and those in auricular fibrillation with or without congestive heart failure. There is no significant difference in the groups that showed deviation from normal weight. This is what might be expected, because a person who is usually underweight might have mild hyperthyroidism while an obese patient might be extremely ill.

*Comparison of Average Cholesterol Values by Age Groups*—In table 4 the values in one hundred and twenty-four cases in which the patients received no iodine are arranged according to decades. The averages show no significant change with age.

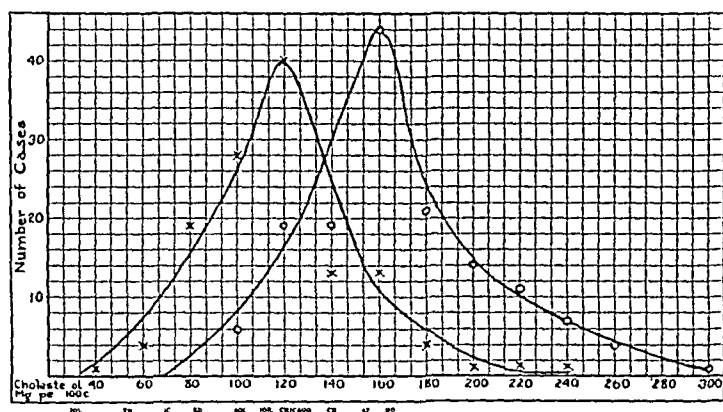


Chart 1—Smoothed frequency curves of cholesterol values in untreated exophthalmic goiter (cross line) and nontoxic goiter (circle line)

*Severe Hyperthyroidism, Auricular Fibrillation and Congestive Heart Failure*—Of interest are the findings in this group of patients. Twenty-four patients with exophthalmic goiter were admitted with auricular fibrillation, sixteen of whom had congestive heart failure (table 5). It is obvious that congestive heart failure is not responsible for the low cholesterol values in view of the low values found in other cases (table 6). This observation is further borne out by the fact that in ten cases of congestive heart failure not associated with goiter in which specimens of the blood were obtained, the average value was 162 mg per hundred cubic centimeters.

While auricular fibrillation occurs frequently in patients who are obviously severely toxic, it is frequently seen in subjects who at first glance appear only slightly activated. The latter fall into a group which Dr. Lahey has termed "the apathetic type." The low cholesterol would seem to indicate that auricular fibrillation is associated with the severity of hyperthyroidism, an accurate estimation of which cannot be arrived at from the basal metabolic rate alone. However, the low cholesterol

values in these cases are associated in a general way with the higher basal metabolic rates (table 5)

In table 6 are listed values in the severely ill patients without auricular fibrillation or congestive heart failure. The patients in this

TABLE 2—*Exophthalmic Goiter. Average Blood Cholesterol Correlated with Deviation from Normal Weight for Patients Not Receiving Iodine Before Admission*

Groups	Cholesterol, Mg per 100 Cc	Average Percentage Deviation from Normal Weight	Average Basal Metabolic Rate, per Cent	Average Pulse Rate	Average Weight in Pounds	Number of Cases
30 per cent or more underweight	128	-37	+52	102	128	10
20-29 per cent underweight	127	-25	+48	113	104	23
10-19 per cent underweight	125	-14	+51	107	112	36
1-9 per cent underweight	121	-6	+41	110	127	25
Normal weight or over	127	+6	+49	109	141	30

TABLE 3—*Exophthalmic Goiter. Correlation of Average Blood Cholesterol with Average Loss of Weight in Patients Not Receiving Iodine Before Admission\**

Groups	Cholesterol, Mg per 100 Cc	Average Basal Metabolic Rate, per Cent	Average Pulse Rate	Average Weight in Pounds	Average Percentage Deviation from Normal Weight	Number of Cases
No loss	137	+44	109	122	-5	12
1-9 pounds loss	130	+49	112	108	-14	20
10-19 pounds loss	126	+49	107	114	-13	48
20-29 pounds loss	118	+46	100	119	-3	12
30-39 pounds loss	122	+50	104	121	-11	14
40-49 pounds loss	123	+49	121	123	-5	8
50 pounds or over	120	+52	95	120	-27	4

\* Loss of weight not recorded in six

TABLE 4—*Exophthalmic Goiter. Average Cholesterol Values by Decades for Patients Not Receiving Iodine Before Admission*

Age Groups	Cholesterol, Mg per 100 Cc	Average Basal Metabolic Rate, per Cent	Average Weight in Pounds	Number of Cases
10-19 years inclusive	113	+49	101	7
20-29 years inclusive	128	+47	119	33
30-39 years inclusive	127	+48	115	38
40-49 years inclusive	113	+48	122	29
50-59 years inclusive	108	+46	108	10
60-69 years inclusive	131	+49	131	7

group were in the so-called thyroid crisis or on the verge of it when they entered the hospital. The low cholesterol values are to be noted.

There were twenty-nine other patients in this series of cases who showed cholesterol values below 100 mg on admission. Fourteen of this group, or nearly one-half, had two-stage operations. Because in only 20 per cent of our cases were multiple stage operations per-

formed and since the decision to perform one or two operations was arrived at without knowledge of the cholesterol determination, the low values were in harmony with the estimate of operative risk, which is,

TABLE 5—*Exophthalmic Goiter Blood Cholesterol in Exophthalmic Goiter with Auricular Fibrillation With and Without Congestive Heart Failure*

Number	Blood Cholesterol, Mg per 100 Cc	Basal Metabolic Rate, per Cent	Pulse Rate	Weight in Pounds	Percentage of Deviation from Normal Weight	Congestive Heart Failure	Compound Tincture of Iodine Before Admission
23638	53	+ 78	132	109	-14	+	0
20926	75*	+ 72	126	122	-10	+	0
21775	77*	+ 84	136	114	-13	+	0
4343	78*	+ 68	148	139	+ 5	+	0
24212	80*	+ 52	108	138	+ 1	+	0
6432	82*	+ 62	92	146	- 5	+	0
21897	82	+ 52	160	104	-22	+	0
22300	84	+ 69	108	112	-25	+	+
22221	85	+104	124	116	- 8	0	+
21025	86*	+ 41	100	77	-44	+	0
23904	93	+ 67	106	154	+10	+	0
22785	97	+ 62	120	156	-10	+	0
22947	105	+ 23	100	153	+17	0	0
23434	111	+ 26	90	120	-27	0	0
23951	118	+ 44	146	117	-12	+	+
23194	119	+ 45	92	104	-24	0	+
21752	123	+ 45	104	176	- 7	0	0
20520	123	+ 51	124	150	+ 0	0	0
20641	128	+ 65	100	138	-24	0	+
23268	134	+ 41	130	72	-36	+	0
24238	151	+ 20	92	113	-24	0	0
21916	154	+ 25	62	165	+17	+	+
23288	162†	+ 32	102	81	-40	+	+
21339	199	+ 69	92	117	-25	+	+
Average	108	+ 54	112	125	-13		

\* Recurrent cases

† Basal metabolism test made a few days later

TABLE 6—*Exophthalmic Goiter Blood Cholesterol in Severe Exophthalmic Goiter in Crisis or on Verge of Crisis*

Number	Blood Cholesterol, Mg per 100 Cc	Basal Metabolic Rate, per Cent	Pulse Rate	Weight in Pounds	Percentage of Deviation from Normal Weight
24268	48*	+46	110	90	-41
21188	68*	+57	110	135	-26
20864	71	+74	142	168	+15
21936	81	+38	120	128	- 5
23594	83	+69	112	86	-43
21267	85	+74	118	151	+17
21253	95	+83	132	102	-19
22899	104	+58	100	104	-18
22348	99	+65	108	150	- 3
Average	82	+66	117	124	-15

\* Basal metabolism test made a few days later

broadly speaking, the severity of thyroid intoxication. Doubtless the decision to perform only one operation in some of these cases was made after marked improvement on the usual preoperative regimen.

*Analysis of Cholesterol Values Over 180 Mg in Exophthalmic Goiter*—Only twenty-two patients were in this group (table 7). Thir-

teen had received iodine before admission, and five were considered to be in a state of remission due to iodine. Pathologic examination showed that chronic thyroiditis was present in two. Only six were known to have received iodine, and of these three showed a cholesterol value of over 180 mg. This represents 2.4 per cent of patients seen who had not received iodine and about 1 per cent of the total number of cases of exophthalmic goiter in which determinations were made on the first day in the hospital.

TABLE 7—*Exophthalmic Goiter Cases Showing Cholesterol Over 180 Mg per 100 Cc on Admission to Hospital*

Case	Sex	Age	Basal Meta- bolic Rate, per Cent	Pulse Rate	Weight in Pounds	Choles- terol, Mg per 100 Cc	Devia- tion from Normal Weight	Com- pound Tincture of Iodine Before Entering	Comment
25697	M	48	+10	84	182	197	+9	++	Iodine remission
24892	F	43	+6	96	125	233	-11	++	Iodine remission
22022	F	35	+4	80	130	202	-8	++	Iodine remission
23073	F	44	+13	82	153	260	+12	++	Iodine remission
23308	F	43	+45	130	165	187	+18		
20986	F	50	+19	112	113	185	-20	0	Thyroiditis, exophthal- mos
24890	F	60	+24	106	131	191	-2	++	
21978	F	28	+34	108	137	186	0	0	Active tuberculosis
22481	F	60	0	86	103	245	-27	0	Spontaneous remission, moderate strumitis
23098	F	55	+24	88	134	219	0	?	Angina
25185	F	61	+18	90	121	184	-12	++	Iodine remission
22746	M	40	+12	110	144	272	+2	++	Iodine remission
21386	M	36	+60	102	112	182	-26	0	
15767	F	44	+30	108	130	193	-8	++	Recurrent
23376	F	49	+52	100	122	186	-13	?	
22958	F	28	+38	98	158	199	+21	++	
24890	F	60	+24	106	131	191	-3	++	
22840	F	33	+24	102	112	185	-10	0	
21339	F	50	+69	92	117	199	-25	++	
20761	F	37	+28	112	129	219	-13	++	
22731	F	30	+44	100	123	182	0	0	No loss of weight
23037	F	48	+27	78	116	213	-17	++	

TABLE 8—*Exophthalmic Goiter Recurrent Hyperthyroidism, Average Cholesterol Determinations in Thirty-Two Cases*

Cholesterol, Mg per 100 Cc	Average Basal Metabolic Rate, per Cent	Average Pulse Rate	Average Weight in Pounds	Average Percentage Deviation from Normal Weight
127	+38	103	130	-7

*Recurrent Hyperthyroidism*—Table 8 lists cases of recurrent or persistent hyperthyroidism. No separate analysis was made in these cases. Most of the patients had taken compound solution of iodine. Six other recurrent cases are listed under the group with auricular fibrillation. Attention should be called to the fact that these six patients had congestive heart failure as well and had not received compound solution of iodine. The highest cholesterol value found in these six cases of recurrent hyperthyroidism with auricular fibrillation and congestive heart failure was 82 mg per hundred cubic centimeters.



*Toxic Adenomatous Goiter* —Sixty-three cases of toxic adenomatous goiter were studied. They were grouped according to whether or not the patients had received iodine before admission (table 9). It is noteworthy that while the average cholesterol values are below the normal range, there is no evident relationship between the basal metabolic rate, pulse rate and weight, such as is shown in the group of cases of exophthalmic goiter. That iodine does not produce such changes should not be inferred from such an analysis, in view of the relative inaccuracy of such a history and the smaller number of cases.

TABLE 9—*Toxic Adenomatous Goiter: Average Cholesterol Values on Admission to Hospital in Cases Grouped According to History of Taking Iodine Previously*

Group	Cholesterol, Mg per 100 Cc	Average Basal Metabolic Rate, per Cent	Average Pulse Rate	Average Weight in Pounds	Average Percentage of Deviation from Normal Weight	Number of Cases
Iodine taken before admission	142	+38	106	119	-11	15
Indefinite history regarding iodine	149	+30	96	131	-17	27
No history of having taken iodine	140	+40	107	129	-7	21

TABLE 10—*Toxic Adenomatous Goiter: Auricular Fibrillation in Toxic Adenomatous Goiter*

Sex	Age	Cholesterol, Mg per 100 Cc	Basal Metabolic Rate, per Cent	Pulse Rate	Weight in Pounds	Deviation from Normal Weight	Congestive Heart Failure	Iodine Before Entry
F	42	71	+61	118	129	-7	+	+
F	65	156*	+65	72	115	-22	0	+
F	50	94	+42	98	138	-2	+	?
F	34	88	+37	150	107	-15	0	0
F	53	179†	+16	108	138	0	0	+
F	58	125	+30	118	155	+13	+	?
F	58	147	+35	120	119	-14	0	+
F	65	99	+33	80	108	-21	+	+
F	62	88	+44	76	112	-13	+	0
Average	54	116	+40	104	125	-9	5	—

\* Long preparation elsewhere

† Borderline toxicity

Five cases showed a cholesterol value below 100 mg per hundred cubic centimeters. All of the patients had auricular fibrillation, four of the five had congestive heart failure. I believe that this is significant and corresponds to the same type of case in exophthalmic goiter. The values for the patients with auricular fibrillation are shown in table 10.

#### NONTOXIC GOITER

One hundred and forty-six patients with nontoxic nodular goiter were examined. Of this group ninety-six showed single nodules, while fifty displayed multiple nodules. These should serve as a control for

toxic cases, except that higher values might be expected at times if the theory that some nodules form in response to a deficient secretion from other parts of the thyroid gland is true. One patient in the group showed myxedema, following the use of thyroid extract, not only did all signs of myxedema disappear, but the goiter was reduced greatly in

TABLE 11—*Nontoxic Goiter Average Cholesterol Values Correlated with Decades*

Age Group	Average Basal Metabolic Rate, per Cent	Average Cholesterol, Mg per 100 Cc	Average Pulse Rate	Average Weight in Pounds	Average Percentage Deviation from Normal
Single Nodules					
15-29	0	162	82	133	+4
30-39	0	169	77	134	0
40-49	+3	182	83	143	+2
50-59	+4	169	87	141	0
60-69	0	234	82	144	-6
Average	+1	178	82	139	
Multiple Nodules					
18-29	0	158	84	124	-2
30-39	+2	166	83	138	-3
40-49	+3	187	82	145	+3
50-59	0	192	82	143	+1
60-69	+7	207	86	142	-2
Average	+3	184	84	139	
Average both groups	+2	180	83	139	

TABLE 12—*Nontoxic Goiter Average Values Correlated with Deviation from Normal Weight*

Deviation from Normal, per Cent	Average Cholesterol, Mg per 100 Cc	Average Basal Metabolic Rate, per Cent	Average Pulse Rate	Average Weight in Pounds	Average Percentage of Deviation from Normal Weight	Number of Cases
Single Nodules						
-20 down	183	+7	80	106	-28	9
-20 to -10	194	+3	81	104	-15	9
-10 to +10	171	+1	81	136	0	51
+10 to +20	164	0	79	157	+16	13
+20 up	181	+2	80	179	+34	8
Multiple Nodules						
-20	165	+22	90	110	-25	5
-20 to -10	175	+1	91	120	-11	8
-10 to +10	188	+1	83	133	0	26
+10 to +20	192	+3	82	165	+15	5
+20 up	196	+2	76	179	+30	6

size (The patient now wears a number 15 collar, whereas he formerly used number 17.)

The wide "scatter" of the values as seen in chart 1 certainly appears to be greater than would be expected in a group of normal persons. Correlation of average cholesterol values with age groups (table 11) suggests strongly that higher levels are found as age advances. The results found on correlating cholesterol values with deviation from normal weight are not striking (table 12). Not a few of the patients

TABLE 13—*Chronic Thyroiditis*

Sex	Age	Cholesterol, Mg per 100 Cc	Basal Meta- bolic Rate, per Cent	Pulse Rate	Weight in Pounds	Devia- tion from Normal Weight	Oper- ated	Comment
F	58	255	-1	90	109	-23	+	
F	52	240	+20	82	107	-19	+	
F	42	191	-15	72	127	-13	+	
F	59	223	-6	84	147	+4	+	
F	46	159	-11	76	140	-1	+	
F	58	189	+15	80	113	-21	+	
F	43	227	+4	80	157	+15	0	
F	51	252	-1	86	108	-27	0	
F	49	181	-18	82	152	0	0	
F	67	236	+5	78	135	-2	0	
F	19	167	+4	88	116	-8	0	
F		191	-14				0	Basal metabolism test per- formed elsewhere
F	51	240	-20	68	141	-10	0	
F	53	244	-9	62	125	-7	0	Mild myxedema
F	49	227	-8	66	134	-2	0	
F	52	208	-15	72	149	+10	0	
F	46	240	-27	68	125	-20	+	Operation 4 months before for drainage of abscess of thy- roid; mild myxedema developed
Average		216	-6	77	130	-8	7	

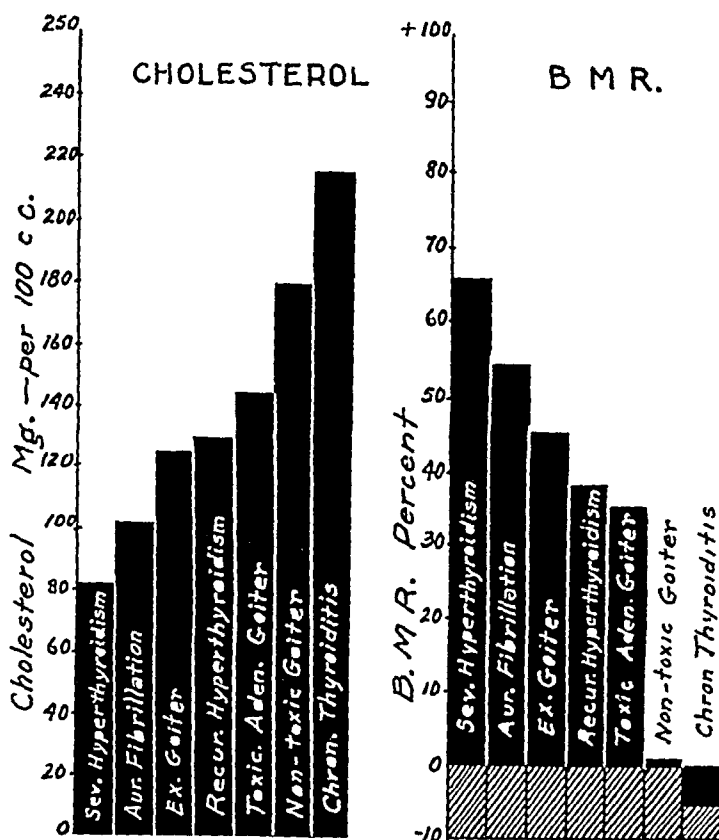


Chart 2—Average cholesterol values and average basal metabolic rates in the various clinical groups of patients with goiter. The group labeled severe hyperthyroidism includes cases of exophthalmic goiter and toxic adenomatous goiter. The group labeled auricular fibrillation includes all those with exophthalmic goiter, recurrent exophthalmic goiter and toxic adenomatous goiter. In the group labeled exophthalmic goiter are placed all cases of exophthalmic goiter, including those with auricular fibrillation or in thyroid crises. Recurrent hyperthyroidism designates recurrent exophthalmic goiter.

showing blood cholesterol values of over 220 mg per hundred cubic centimeters showed evidence of marked vascular disease. Further analysis of this group will be presented in a later paper.

#### CHRONIC THYROIDITIS

Some cases of myxedema are clearly caused by chronic thyroiditis, the most severe form of which is Riedel's struma. Fifteen such cases were encountered, in seven of which operation for tracheal pressure was performed and the diagnosis thus established. Two of the fifteen patients showed mild myxedema, and operation was not performed. Subsequent thyroid therapy has relieved these two patients.

Certainly, if there is a borderline state between normal thyroid function and nonevident clinical hypothyroidism, it should be produced by this type of thyroid disease. The cholesterol values found in this group are listed in table 13.

#### COMMENT

The purpose of this paper is to present values obtained for blood cholesterol in toxic and in nontoxic goiter before treatment. References to the literature have been listed elsewhere.<sup>1</sup> Subsequent papers appearing since then will be referred to in the subsequent reports of this study, which will deal with the results of treatment and with further observations in myxedema and other clinical conditions.

In chart 2, the average values of the toxic and nontoxic groups are shown graphically along with the average metabolic rates in those groups. Scrutiny of this chart clearly demonstrates the general reciprocal relationship between the mean cholesterol values and the mean basal metabolic rates. If the mean values for cholesterol and the basal metabolic rate in myxedema as reported from this laboratory<sup>1</sup> were added to this chart, a still more striking relationship would be seen (average cholesterol, 336 mg per hundred cubic centimeters, average basal metabolic rate, minus 33 per cent—twenty-three cases).

#### SUMMARY AND CONCLUSION

- 1 The blood cholesterol during fasting was determined as a routine in five hundred and five cases of thyroid disease, along with the pulse, the weight and the basal metabolic rate.
- 2 The lowest average values for blood cholesterol are found in patients in or near thyroid crises.
- 3 Auricular fibrillation in toxic goiter is associated with the next lowest average level of cholesterol.
- 4 The average cholesterol value in all types of exophthalmic goiter is lower than in toxic adenomatous goiter.

5 Recurrent hyperthyroidism is associated with cholesterol values that are almost as low as those in exophthalmic goiter

6 The average cholesterol value in nontoxic goiter is normal, although the scatter is wider than expected. Age appears to raise the blood cholesterol in these cases

7 Chronic thyroiditis is associated with higher average values than in any other thyroid disease except myxedema

8 The level of the blood cholesterol and the basal metabolic rate bear a reciprocal relationship when judged by average values

# INTRAVENOUS PRESSURE

## I NEW METHOD OF DETERMINATION

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Intravenous pressure may be estimated clinically by either direct or indirect methods. The former is accomplished by the use of a hollow needle or trocar inserted into a vein and connected with a suitable manometer, while the indirect methods are based on the principle of measuring the external pressure necessary to obliterate the vein so that it is no longer visible above the surface of the skin.

Determination of intravenous pressure by direct methods has been described by Moritz and von Tabora,<sup>1</sup> Schott,<sup>2</sup> Bedford and Wright<sup>3</sup> and others. Such direct methods, while more accurate, have certain disadvantages which preclude their general use in clinical medicine. The more important objections are the impossibility of frequent determinations in the same patient, the necessary prerequisite of strict asepsis, the possibility of formation of clot in the needle, which interferes with accurate readings and the difficulty sometimes encountered in puncturing a vein obscured by fatty tissue in obese persons. We have also had apprehensive patients who could not rest quietly or who became frightened by the venous puncture, with the result that the venous pressure was elevated considerably.

The indirect or bloodless methods are free from most of these objections, but the prevailing procedures are attended by other disadvantages which prevent their adoption for universal use in routine examination of patients. Attempts have been made to overcome some of the disadvantages inherent in such methods by Frey,<sup>4</sup> von Basch,<sup>5</sup>

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This research was aided by the Emil and Fanny Wedeles Fund of the Michael Reese Hospital for the Study of Diseases of the Heart and Circulation.

1 Moritz and von Tabora. *Deutsches Arch f klin Med* **98** 475, 1910.

2 Schott, E. *Deutsches Arch f klin Med* **108** 537, 1912.

3 Bedford, D E, and Wright, S. *Lancet* **2** 106, 1924.

4 Frey, A. *Deutsches Arch f klin Med* **73** 511, 1902.

5 von Basch, S. *Arch di sc biol* **2**:117, 1904-1905.

Hooker,<sup>6</sup> Eyster<sup>7</sup> and others, but certain objections still remain, the most serious being that the end-point is not sharp, and that correct estimations are therefore difficult to obtain unless they are made by those who are expert with the particular device used. Another important disadvantage is the impossibility of applying such methods to obese persons in whom the veins are not visible above the surface of the skin. Indirect methods are still further limited by certain possibilities for error because of inherent defects in the construction of the apparatus or by the fact that the end-point must be determined quickly.

It is not our purpose to give a detailed review of the methods now in use, because our procedure is based on a new principle. We believe that the method to be described eliminates most of the objections mentioned, and that it has the additional advantage of a sharp end-point which can be read without hurry.

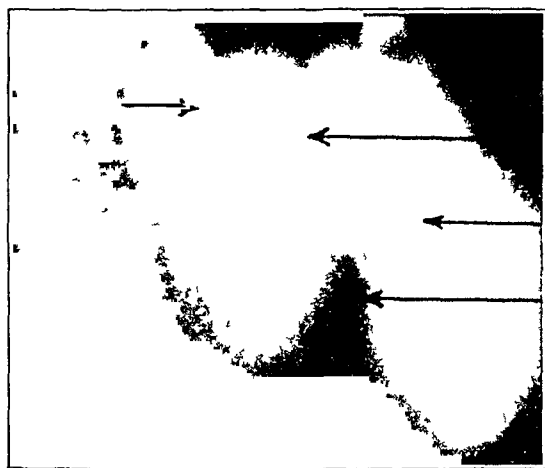


Fig 1—Appearance of veins on transillumination, indicated by arrows

As in other indirect methods, it is necessary to proceed under basal conditions, which consist of placing the patient at rest for ten minutes in a horizontal or semirecumbent position. The arm and hand to be examined are supported horizontally by a pillow and held at a level which corresponds to the point of entrance of the vena cava into the right auricle. Following the suggestion of Eyster, we estimate this point to be in the fourth interspace, at the junction of the anterior and middle third of the anteroposterior diameter of the thorax. This furnishes a fixed point for estimating the venous pressure, so that future determinations can be compared, and gives, in addition, the pressure at the level at which the veins enter the heart.

6 Hooker, D R., and Eyster, J A E. *Bull Johns Hopkins Hosp* **19** 274, 1908

7 Eyster, J A E. *The Clinical Aspects of Venous Pressure*, New York, The Macmillan Company, 1929

The method itself is based on the principle that the superficial veins on the dorsum of the hand can be easily visualized in a darkened room by placing a small light, such as an ordinary pocket flashlight, against the palmar surface, preferably in the interosseous spaces.<sup>8</sup> The superficial veins by this transillumination appear as black bands which can be obliterated by moderate pressure, and thus distinguished from shadows cast by ligaments.

The mouth of a small glass funnel is covered by a thin rubber dam held securely in place by a thread tied tightly in a previously pre-

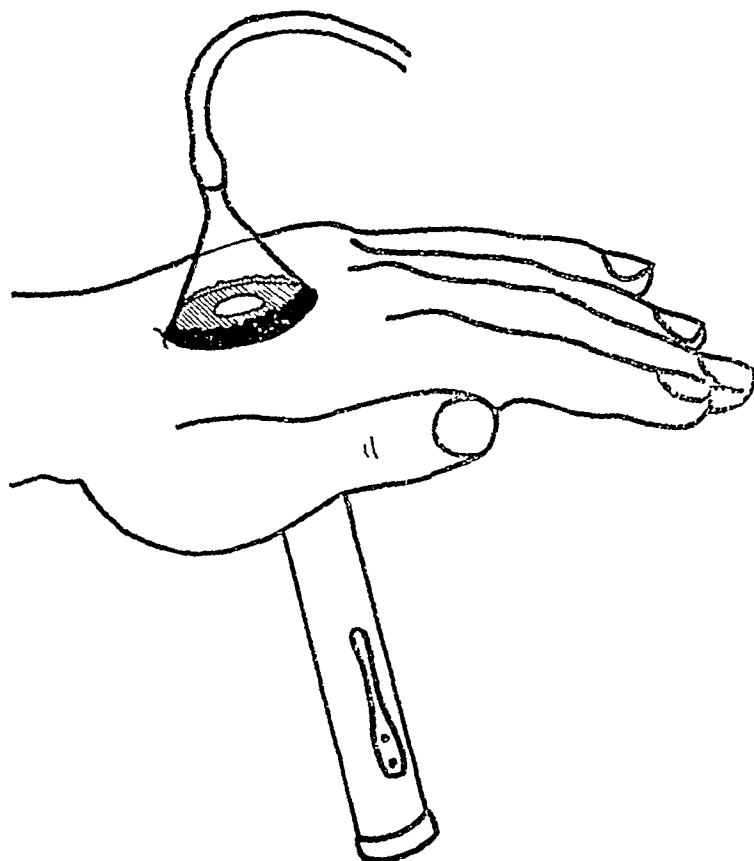


Fig 2—Diagram of arrangement used for new method of measuring venous pressure

pared groove near the rim. A small hole is then cut in the center of the rubber dam, through which the vein to be examined is visualized. Such a vein is previously selected in a darkened room in the manner indicated, and its location marked. The surface of the rubber dam is then covered with rubber cement, and the funnel is placed on the dorsum of the hand so that the previously selected vein is seen through the aperture in the rubber. The funnel is held in place by moderate

<sup>8</sup> This was suggested by observing the appearance of the veins during transillumination of a breast by Dr. Max Cutler.



pressure until the rubber is adherent to the skin. This makes an airtight seal. The tip of the funnel is then connected by rubber tubing to a suitable water manometer which is so graduated that pressure may be read in millimeters of water. The room is again darkened, or a black cloth is placed over the head of the observer, and the light is placed against the palmar surface of the hand in order to visualize the dorsal vein within the aperture of the rubber dam. The air pressure is then slowly raised in the instrument by a suitable rubber bulb—with the leak-valve shut—until the vein under examination becomes obliterated as a result of the external compression. It is important to distinguish two stages, the first is the obliteration of the vein, and the second, further blanching of the skin. We have selected the former as the end-point at which the pressure is read off in the manometer in millimeters of water. A diagram of the set-up is shown in figure 1,

### *Venous Pressure*

Name	Diagnosis	Direct Reading (Mm H <sub>2</sub> O)	Indirect Reading (Mm H <sub>2</sub> O)
H S	Rheumatism, mitral stenosis and insufficiency, moderate decompensation	135	135
I R	Normal	55-60	50
B P	Noncardiac	70	75-80
A C	Noncardiac	65	65
K	Hypertensive heart disease, compensated	45	40-45
S P	Noncardiac	65	60-65
C M	Noncardiac	60	70-75
W L	Noncardiac	90	105
J L	Noncardiac	60	60
A S	Hypertensive heart disease, moderate decompensation	110	115
G D	Noncardiac	85	85-90
R G	Hypertensive heart disease, obesity, slight decompensation	100	90

and a photograph of the appearance of the veins on transillumination is shown in figure 2.

We were careful to avoid error by covering the head of the observer with a black cloth, while another person noted the height of the water column in the manometer tube. Several readings were taken for each patient, and the end-point was announced by signal to the person reading the manometer. A series of twelve patients were examined by this procedure, and the results were later compared with those obtained by the direct method (table)<sup>9</sup>. These patients consisted of persons with cardiac disease and a group suffering from other than cardiac disease. An obese patient whose veins were not visible above the surface of the skin and who could not be examined by the Eyster method is included in this series. The device has also been tried in

<sup>9</sup> The apparatus for this has been described elsewhere (Katz, L. N., Hamburger, W. W. and Rubinfeld, S. H. Observations on Oxygen Therapy II. Changes in the Respiration and Circulation, *Am J M Sc* **184** 810 [Dec] 1932.)

colored patients and has been found practicable. The table shows that a high degree of accuracy is possible when the results of our indirect method are compared with those obtained by the direct method.

We are presenting this report for the purpose of describing a new principle in the estimation of venous pressure. We believe that with minor improvements in the instrument and technic the method can be adopted for general clinical use. The advantages over other indirect methods are its greater accuracy, the simplicity of the apparatus and the possibility of its use in obese and other patients in whom other indirect or direct procedures may fail. We are projecting a series of experiments in an attempt to use this method clinically in order to determine its practicability.

# TRANSIENT METHEMOGLOBINEMIA DUE TO AMMONIUM NITRATE

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Toxic manifestations due to the administration of large doses of the nitrates are well known. This is particularly true of bismuth subnitrate<sup>1</sup>. The most striking finding in such patients is methemoglobinemia with severe cyanosis. The factor responsible is a reduction of the nitrate to the nitrite with subsequent transformation of the hemoglobin to methemoglobin.

In 1926 Jacobs and Keith<sup>2</sup> suggested the use of ammonium nitrate as the least disagreeable and the most effective of the acid-producing salts to be used as a diuretic. They employed it extensively at the Mayo Clinic without any detrimental effects.

In 1928 Barker and O'Hare<sup>3</sup> reported for the first time the appearance of severe cyanosis in a patient with nephrosis who had received 15 Gm of ammonium nitrate a day for ten days. They attributed the condition to methemoglobinemia, although spectroscopic examination of the blood was not made.

In 1929 Eusterman and Keith<sup>4</sup> reported the occurrence of transient methemoglobinemia in two patients who had received ammonium nitrate. Their first case was in a man 32 years of age with edema of renal origin complicating a gastro-enterostomy that did not function properly. He suffered from severe gastric and intestinal distress. Following the administration of 54 Gm of ammonium nitrate during a period of ten days, marked cyanosis developed which was shown spectroscopically to be due to methemoglobinemia. In addition, the patient was very weak and irrational and fainted once. When the drug was discontinued he returned to his previous condition within forty-eight hours. The second patient was a woman, 47 years of age, with marked edema and ascites, probably secondary to syphilitic cirrhosis of the liver, who suf-

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From the Medical Division of the Montefiore Hospital

This work was done under the auspices of the Hilda Stich Stroock Fellowship

1 Beck, E. G. Toxic Effects from Bismuth Subnitrate, *J. A. M. A.* **52** 14 (Jan. 2) 1909

2 Jacobs, M. F., and Keith, N. M. The Use of Diuretics in Cardiac Edema, *M. Clin. North America* **10** 605 (Nov.) 1926

3 Barker, M. H., and O'Hare, J. P. The Use of Salvrigan in Edema, *J. A. M. A.* **91** 2060 (Dec. 29) 1928

4 Eusterman, G. B., and Keith, N. M. Transient Methemoglobinemia Following Administration of Ammonium Nitrate, *M. Clin. North America* **12** 1489 (May) 1929

fered from severe constipation as well. On two occasions cyanosis due to methemoglobinemia developed, once after a total of 24 Gm given 10 Gm a day, and again after a total of 89 Gm given 8 Gm a day. In normal patients and in dogs the authors were unable to produce methemoglobinemia with the drug. They regard the reduction of the nitrate to the nitrite in the bowel as an abnormal process.

In 1928 Christian,<sup>5</sup> in a discussion of the use of ammonium nitrate as a diuretic, mentioned the fact that he saw a patient in whom methemoglobinemia developed after the administration of the drug. He does not state the diagnosis, the predisposing factors or the amount given.

In 1930 Keith, Whelan and Bannick,<sup>6</sup> in a complete study of nitrate diuresis, reported another case of methemoglobinemia. Their patient suffered from chronic nephrosis and was in addition very constipated. The methemoglobinemia developed after the patient had received 10 Gm of the drug a day for twelve days.

In all the patients the symptoms and signs cleared up rapidly after the drug was discontinued.

Since 1929 ammonium nitrate has been used as a diuretic and as an adjuvant to diuresis at the Montefiore Hospital. It is given in gelatin-coated tablets weighing 0.5 Gm each, or as a 40 per cent aqueous solution in doses of 6 to 8 Gm per day. Only occasionally is this dose exceeded. It has been found the least disagreeable and the most effective of the acid-producing salts. In two years of its use no toxic manifestations were seen. During this time more than 65,000 Gm of ammonium nitrate was consumed in a medical service which has a large number of patients suffering from cardiovascular diseases. The substance has been tested for nitrites as impurities, and none were found. Recently, within a short time, in the following four patients severe cyanosis due to methemoglobinemia developed after the administration of ammonium nitrate.

#### REPORT OF CASES

**CASE 1—History**—S. B., a Russian Jew, 45 years of age, enjoyed good health until his present illness. In September, 1930, he began to complain of progressively increasing shortness of breath and noticed swelling of the lower extremities. The result of an examination of the urine for albumin was 4 plus. He entered a hospital shortly thereafter, where a diagnosis of nephrosis was made. Under high protein feeding and the administration of diuretics there was slight improvement in his condition. He was transferred to Montefiore Hospital on March 18, 1931.

**Physical Examination**—The patient was a well developed, middle aged, ambulant man, complaining chiefly of weakness and swelling of the lower extremities. There was decided oxycephaly. The eyegrounds showed medullated nerve fibers, but no

5 Christian, H. A., in discussion on Keith, N. M., Whelan, M., and Bannick, E. G. *Diuretic Action of Nitrates and Their Use in the Treatment of Dropsy*, Tr. A. Am. Physicians **43** 290, 1928.

6 Keith, N. M., Whelan, M., and Bannick, E. G. *The Action and Excretion of Nitrates*, Arch. Int. Med. **46** 797 (Nov.) 1930.

other changes. The heart was slightly enlarged to the left, the rhythm was regular, and there was an accentuation of the second aortic sound. The blood pressure ranged from 124 systolic and 90 diastolic to 170 systolic and 110 diastolic. There was evidence of a right hydrothorax. Over the abdominal wall was a network of collateral circulation that was more prominent on the right side. The liver was firm and reached to the level of the umbilicus. Edema of the lower extremities was marked.

*Laboratory Data*—On a limited fluid intake, he voided from 400 to 600 cc of urine daily, which contained on an average 2.5 per cent of albumin. The specific gravity ranged up to 1.035. Hyaline and granular casts and double refractive bodies were present. The test for Bence-Jones protein was negative. Chemical examination of the blood showed a marked diminution of the serum albumin and globulin to 17 and 27 mg per hundred cubic centimeters, respectively. The fat content increased to 2.04 mg. Later, under treatment, the serum albumin and globulin rose to 28 and 38 mg, respectively. The blood urea nitrogen and creatinine were normal. Thoracentesis of the right side of the chest on several occasions yielded a milky fluid which contained 0.5 per cent protein and 0.2 per cent fat. Inoculation of guinea-pigs with the aspirated fluid from the chest was negative for tuberculosis. The Bennhold test for amyloid disease was negative.

*Diagnosis*—It was felt that the underlying condition was chronic glomerulonephritis and that the patient was in the nephrotic phase. The large liver and the collateral circulation were accepted as evidence of a lesion about the entrance of the inferior vena cava through the diaphragm, perhaps an obliterative pleurisy or a tuberculous process. Roentgen examination showed diffuse proliferative changes in this region.

On the death of the patient several months later, the true diagnosis was disclosed. There was an old thrombosis of the inferior vena cava extending into the renal veins on both sides. The lumen of the veins was completely obliterated. There was evidence of an increased collateral circulation in the perirenal tissue and in the veins of the renal capsule. The latter stripped easily and left a smooth, yellow, injected surface. The consistence was flabby, and the cut surface smooth and greasy. There was a sharp contrast between the yellow cortex and the red medulla. On microscopic section the kidneys showed diffuse fatty degeneration of the parenchymatous elements.

The right lung was reduced to about one-fourth the normal size and covered with thin sheets of fibrin. The lower lobe was partially collapsed. Between it and the diaphragm was a large encapsulated collection of soft, semitranslucent gelatinous material, not unlike the postmortem "chicken fat" clot. There was in addition a moderate amount of milky fluid. The whole lesion was apparently an old encapsulated pleurisy or empyema that had undergone extensive change.

A more complete clinical and anatomic description of this case will appear in a separate report.

*Course and Treatment*—The patient was maintained with varying success on urea, occasional doses of salyrgan and ammonium nitrate in an attempt to control the edema. By Oct 6, 1931, he had received 696 Gm of ammonium nitrate at the rate of 6 Gm a day almost continuously for nearly eighteen weeks. It was then decided to increase the dose to 9 Gm a day. After two weeks of therapy with the larger dose severe cyanosis of the hands, feet and face suddenly developed. The mucous membranes had an ashen blue, almost violaceous color. The patient felt weak and complained of substernal oppression. The blood pressure was 150 systolic and 94 diastolic, the pulse rate was 90. Neurologic examination showed hyperreflexia of both the upper and the lower extremities, bilateral, inexhaustible.

ankle clonus and a bilateral Babinski and a bilateral Hoffman sign in addition to numerous twitching movements of the fingers

All medication except inhalation of oxygen was discontinued. By the next morning this dramatic picture had disappeared, and the patient was his former self. He was not given the drug again. Blood drawn at the height of the cyanosis was dark chocolate brown and did not change on shaking and exposure to the air. The urea nitrogen was 17 mg per hundred cubic centimeters, and the carbon dioxide 50 per cent by volume. The urine showed the usual amount of albumin and double refractive bodies. The blood count showed 4,200,000 red blood cells with 75 per cent hemoglobin. Unfortunately, the blood was not examined spectroscopically for methemoglobin. The clinical picture of sudden onset and rapid disappearance of cyanosis and the chocolate brown color of the blood leave little doubt as to the diagnosis of methemoglobinemia.

*Summary*—A man, 45 years old, with marked albuminuria and edema due to bilateral occlusion of the renal veins simulating clinically the picture of a lipoid nephrosis was able to tolerate 696 Gm of ammonium nitrate given 6 Gm a day for eighteen weeks. Following the same medication administered 9 Gm a day severe methemoglobinemia developed in two weeks.

*CASE 2—History*—M. A., a Turkish Jew, 48 years of age, was admitted to Montefiore Hospital on May 29, 1931. For at least four years prior to this time he had been complaining of weakness, shortness of breath and swelling of the lower extremities. On repeated admissions to other hospitals his illness had been diagnosed as chronic glomerulonephritis.

*Physical Examination*—The patient was a well developed and well nourished, but rather pale man, comfortable and ambulant. There was bilateral neuroretinitis, without much disturbance in vision. The heart was moderately enlarged to the left, showing on fluoroscopy involvement chiefly of the left ventricle. The blood pressure ranged from 110 systolic and 80 diastolic to 160 systolic and 90 diastolic. The lungs were clear. No abdominal viscera were palpable. There was marked pitting edema of the lower extremities extending up to the knees.

*Laboratory Data*—There was moderate polyuria with excretion of from 1,500 to 2,000 cc in twenty-four hours. The specific gravity of the urine was fixed between 1.013 and 1.017. From 5 to 6 Gm of albumin per liter was present. Hyaline and granular casts and red blood cells were found in the urinary sediment. Chemical examination of the blood showed a urea nitrogen of 40 mg per hundred cubic centimeters, creatinine, 37 mg, cholesterol, 250 mg, serum albumin, 1.87 mg, and serum globulin, 3.36 mg. There was moderate secondary anemia with a count showing 2,980,000 red blood cells and 56 per cent hemoglobin (Sahli). The Bannhald test for amyloid disease showed 40 per cent retention of the dye after one hour, which is presumptive evidence of amyloidosis.

*Diagnosis*—The diagnosis was chronic glomerulonephritis with a nephrotic component, moderately severe renal insufficiency and probable amyloidosis.

*Course and Treatment*—Persistent edema of the lower extremities required diuretic therapy for relief. For a time the patient was given from 40 to 60 Gm of urea a day with beneficial results. On Oct 21, 1931, he was given 2 Gm of ammonium nitrate three times a day. He had never received this medication before. During the following eight days he received a total of 50 Gm. On Oct 29, 1931, in the course of several hours severe cyanosis developed. His face, hands and feet were a grayish, indigo blue. Particularly striking were the mucous membranes of the mouth and lips. He complained chiefly of headache and weakness. Respiratory distress was conspicuous by its absence. On attempting to leave the bed he collapsed. He was orientated, and his sensorium was clear. Hyperreflexia of the

extremities, slight ankle clonus and a positive Babinski sign on the left side were noted during the height of the cyanosis. A tentative diagnosis of methemoglobinemia due to ammonium nitrate was made. A specimen of blood taken for examination was dark reddish brown. Methemoglobin was identified spectroscopically. During this episode the carbon dioxide-combining power was 26.5 per cent by volume, the urea 73.5 mg per hundred cubic centimeters, and creatinine, 5.2 mg.

All medication was discontinued, and the patient was placed in an oxygen tent for several hours. It is doubtful whether this last measure was of any value. In twelve hours the cyanosis had disappeared, and the patient felt much as he did before the onset of the attack. The abnormal neurologic findings had disappeared. It was interesting to compare the color of samples of venous blood as the cyanosis receded. The dark reddish-brown color of the earlier specimens, which on shaking and exposure to air failed to turn a lighter red, was replaced by color and behavior which approached the normal.

The results of subsequent chemical examinations of the blood were not significantly different from those obtained during the period of methemoglobinemia. The carbon dioxide-combining power rose to 30 per cent by volume and later to 50 per cent.

Because of the already existing severe acidosis and increasing renal insufficiency, it was not deemed advisable to try again other acid-producing salts.

*Summary*—In a man 48 years old man with chronic glomerulonephritis and renal insufficiency severe methemoglobinemia suddenly developed, following the administration of 50 Gm of ammonium nitrate in eight days.

*CASE 3—History*—B. S., an elderly woman, 73 years of age, was admitted to the hospital on Oct 17, 1931, with complaints of dyspnea and precordial pain of four years' duration and swelling of the lower extremities of two years' duration.

*Physical Examination*—The patient was well developed and well nourished. There were an ashen gray pallor of the face and a contrasting cyanosis of the lips. The heart was markedly enlarged to the left, and its base was broadened on percussion. A loud systolic murmur overshadowed both apical sounds. The sounds at the base were poorly heard. The blood pressure was 102 systolic and 60 diastolic. There were signs of pulmonary congestion and thickened pleura at the bases of the lungs. The edge of the liver was palpable at the level of the umbilicus. The spleen was also slightly enlarged. There was marked edema of the lower extremities up to the sacrum.

*Laboratory Data*—The result of examination of the urine for albumin was 2 plus, its specific gravity was fixed between 1.012 and 1.018. Occasional hyaline casts were present. The blood urea nitrogen ranged between 20 and 32 mg per hundred cubic centimeters. The electrocardiogram showed auricular fibrillation with a slow ventricular rate.

*Diagnosis*—The diagnosis was antecedent hypertension with disease of the coronary artery, multiple myocardial infarctions, congestive heart failure and arteriosclerosis of the kidneys.

*Course and Treatment*—On admission to the hospital the patient weighed 73.6 Kg. Following restriction of fluids, a salt-poor diet, the administration of 6 Gm of ammonium nitrate daily and two injections of salyrgan, her weight dropped to 60 Kg in nine days. Edema of the lower extremities had practically disappeared. On Oct 26, 1931, diuretic therapy was discontinued because of a sudden chill and a rise in temperature to 102.5 F. There was no change in the cardiac condition, and the picture was attributed to an acute bronchitis. The elevation in temperature lasted about one week. At the end of this time the patient

was again placed on ammonium nitrate as a diuretic to supplement the action of salyrgan. On the evening of Dec 13, 1931, she was noted to be diffusely cyanotic, although there were no additional symptoms. An hour later she began to complain of severe headache and of feeling uncomfortable. The dyspnea previously present was not increased. The pulse rate was 84 and the blood pressure 110 systolic and 44 diastolic. There was a striking deep blue cyanosis over the entire body, which was most marked on the lips and the visible mucous membranes. Under artificial illumination there was a greenish tinge to the cyanosis. No abnormal neurologic signs were elicited. A specimen of venous blood was dark reddish brown and did not change on shaking and exposure to the air. Methemoglobin was demonstrated spectroscopically.

All medication was discontinued. In twelve hours the patient was much improved, and in twenty-four hours all cyanosis had disappeared. The course since that time has been uneventful. During the cyanotic phase, the carbon dioxide-combining power of the blood was 31.5 per cent by volume. It rose three days later to 52 per cent.

*Summary*—In a woman, 73 years old, with disease of the coronary artery, congestive heart failure and renal arteriosclerosis marked methemoglobinemia developed after the ingestion of 6 Gm of ammonium nitrate a day for forty-two days, a total of 252 Gm.

*CASE 4—History*—L. B., a Jewish woman, 65 years of age, complained of dyspnea and weakness of three years' duration. In 1930 midtibial amputation of the left leg was performed because of arteriosclerotic gangrene. Diabetes mellitus was discovered at that time. On Feb 9, 1931, she was admitted to Montefiore Hospital because of tingling and numbness in the fingers of both hands.

*Physical Examination*—The patient was an emaciated woman confined to bed. The eyes showed bilateral lenticular opacities and numerous pinpoint-sized absorption spots and hemorrhages in the retinas. The right half of the chest was smaller than the left, and there were signs of a fibroid tuberculosis in both lungs, more on the right side. The heart was slightly enlarged to the left. The second aortic sound was accentuated, and the blood pressure was elevated to 180 systolic and 80 diastolic. There was marked sclerosis of all the peripheral palpable vessels. The edge of the liver was barely felt at the costal border. The fingers and toes were moderately cyanosed. The knee jerk and ankle jerk of the remaining extremity were not obtained. The biceps and triceps reflexes were very weak.

*Laboratory Data*—The specific gravity of the urine was fixed between 1.013 and 1.015. Albumin 2 plus and granular and hyaline casts were nearly always present. Glycosuria was found occasionally. The blood sugar fluctuated between 300 and 500 mg per hundred cubic centimeters and the urea nitrogen between 18.5 and 28 mg. A mild secondary anemia was present.

*Diagnosis*—The diagnosis was generalized arteriosclerosis, diabetes mellitus, hypertension, arteriosclerotic heart disease, fibroid tuberculosis, compensated arteriosclerosis of the kidneys and status after amputation of the leg.

*Course and Treatment*—The patient was placed on a diabetic diet and was given 20 units of insulin daily. On Oct 28, 1931, signs of congestive heart failure were noted. She was given 2 Gm of ammonium nitrate three times a day, with a favorable response. On Dec 11, 1931, she complained of headache, nausea and dizziness. The episode was transitory, and no immediate cause could be found. Three days later she again complained of headache and nausea. This time a moderate generalized cyanosis was noted in contrast to the usual pallor. The color was a darker blue than in cardiac cyanosis. No abnormal neurologic reflexes were noted. A specimen of blood taken at this time was dark chocolate brown.



and did not change on shaking and exposure to the air. The ammonium nitrate was discontinued, and within twelve hours she returned to her previous status. The episode was interpreted as a mild methemoglobinemia. The total amount of ammonium nitrate taken was 6 Gm a day for forty-six days.

*Summary*—In a 65 year old woman with marked arteriosclerosis, arteriosclerotic heart disease, diabetes mellitus and impaired renal function, mild methemoglobinemia developed following the administration of 276 Gm of ammonium nitrate in forty-six days.

#### COMMENT

In case 1 the diagnosis of methemoglobinemia was not suspected at the beginning. The blood was not examined spectroscopically, but its dark chocolate brown color and its failure to turn to a lighter red on shaking and exposure to the air were noted at the time. In the other patients the blood behaved similarly. The presence of methemoglobin was confirmed spectroscopically.

It is interesting to note that in the nine cases reported in the literature, including the four reported here, seven patients had renal lesions. Although gastro-intestinal dysfunction is emphasized as an important factor,<sup>4</sup> it was absent in my four patients. Keith and his co-workers<sup>6</sup> have shown that patients with renal insufficiency who have an increased nitrate content in the blood and delayed excretion in the urine have no particular tendency to develop methemoglobinemia. The reduction of nitrate to nitrite probably occurs in the gastro-intestinal tract, but how it is brought about and how it may be prevented in patients receiving ammonium nitrate are at present not understood.

In the previous reports on the toxic action of ammonium nitrate the presence of ankle clonus, hyperreflexia and a positive Babinski sign in the patients during the time they were markedly cyanosed had not been noticed. These neurologic manifestations are probably the result of a cortical irritation arising from the accompanying anoxemia.

The occurrence of transient methemoglobinemia as a toxic manifestation has not led my associates and me to discontinue the use of ammonium nitrate. It is still the best of the acid-producing drugs at our disposal. Discontinuance of the drug at the first indication of cyanosis is the only treatment necessary. When the clinical condition of the patient necessitates the administration of ammonium nitrate in large doses over a longer period, we now omit the drug on every fifth or sixth day. In very susceptible patients it might be advisable to resort to ammonium chloride rather than to the nitrate.

#### SUMMARY

The reported instances of transient methemoglobinemia due to ammonium nitrate are reviewed, and four additional cases are reported. An unusual feature in two of these was the evidence of cortical irritation during the height of the cyanosis.

# ENDEMIC NUTRITIONAL EDEMA

## II SERUM PROTEINS AND NITROGEN BALANCE

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In the preceding paper<sup>1</sup> the clinical findings in thirty-one patients with edema, believed to be nutritional in nature, are reported. In addition to an initial determination of the serum proteins in thirty-one patients with edema, repeated determinations were made in eleven cases over periods of from a few weeks to more than a year, under varying conditions of diet and treatment. Studies of nitrogen balance were made in two cases. The results of these studies are reported in this paper.

### METHODS

With two exceptions, the subjects were studied and followed exclusively in the outpatient department.

*Serum Proteins*—The initial determinations of serum protein were made in some instances at the time the patient was first seen, more often they were made a few days later, and frequently at a time when the edema was lessening. The blood was obtained after an overnight fast or several hours after a light breakfast. It was drawn without stasis or exposure to the air, transferred to a clean centrifuge tube under oil, allowed to clot and the clot allowed to retract. The serum was pipetted off after centrifuging. In the first few cases the total serum proteins alone were determined by the refractometer. In most of the cases the albumin and globulin fractions were separated by the method of Howe,<sup>2</sup> using 22.5 per cent sodium sulphate. This procedure was carried out in a constant temperature box in which all the apparatus and reagents were kept at 37 C. After precipitation the samples were allowed to stand over night. Cloudy filtrates were refiltered until clear or were discarded. In a few of the earlier cases the total protein, albumin and globulin were determined by the colorimetric method of Greenberg.<sup>3</sup> In the

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1 Youmans, John B., Bell, A., Donley, D., and Frank, H. Endemic Nutritional Edema. I. Clinical Findings and Dietary Studies, *Arch. Int. Med.* **50**: 843 (Dec.) 1932.

2 Howe, P. E. The Use of Sodium Sulphate as the Globulin Precipitant in the Determination of Proteins in the Blood, *J. Biol. Chem.* **49**: 93, 1921.

3 Greenberg, D. M. The Colorimetric Determination of the Serum Proteins, *J. Biol. Chem.* **82**: 545, 1929.

majority the total nitrogen of the serum and the albumin nitrogen of the filtrate were determined by the macro-Kjeldahl method. Distillation was carried out without transfer to a separate flask, distilling into fiftieth-normal acid and titrating with fiftieth-normal sodium hydroxide, using alizarin as the indicator. All determinations were made in duplicate and checks were made on the reagents. The total protein nitrogen was calculated by subtracting the nonprotein nitrogen, determined separately, from the total nitrogen. Albumin nitrogen was represented by the difference between the nitrogen of the filtrate and the nonprotein nitrogen. The factor 6.25 was used to convert the figures for nitrogen to protein. Globulin was calculated by the difference between the total protein and albumin.

Studies of nitrogen balance were made in two of the cases (cases 16 and 17) as follows. On admission the patient was placed on a diet corresponding as closely as possible in amounts and kind of food to that which had been eaten at home and which had previously been recorded.<sup>1</sup> The composition of these diets is given in the presentation of the results. Each day's diet was prepared in duplicate in the diet kitchen and weighed. One was given to the patient. The other was sent to the laboratory where the total food for the day was weighed, ground up together and dumped into a large volume of sulphuric acid. Nitrogen was determined on aliquot samples by the usual Kjeldahl method. The food not eaten by the patient was carefully saved, weighed and sent to the laboratory, where its nitrogen content was determined in a similar manner. The urine and stools were passed directly into weighed containers, carefully collected daily and sent to the laboratory. The stools were weighed, wet ashed as already described, and the nitrogen determined on aliquot samples. The complete collection of the urine was controlled by determining the creatinine content of the twenty-four hour specimen. Nitrogen determinations were made in the usual manner. Following a preliminary period on this regimen the experimental periods were begun. To separate the feces belonging to each period the stools were marked by administering a capsule of carmine lake (0.6 Gm.) at 1 p. m. on the last day of each period, and the appearance of the carmine marked the end of that period. When determinations for a single day were made, no attempt was made to separate the stools with carmine, and all stools within a twenty-four hour period were included in the previous day's determinations. After a three to four day period on the diet with a low protein content, a diet of high protein content was given. In case 17 the low protein period was followed by a three day period of low protein diet plus brewers' yeast (15 Gm. daily). This period was in turn followed by a two day period of low protein diet without yeast before the diet with a high protein content was begun. The patients were weighed daily before breakfast and the amount of edema estimated frequently, usually during the afternoon. Determinations of the serum protein were made at suitable intervals. Unfortunately it was necessary to confine the patients to bed during the greater part of the time, in order to insure accuracy in the intake of food and collection of specimens. During the latter part of the study they were allowed to spend some time in a bedside chair.

#### EXPERIMENTAL RESULTS

There are considerable differences in the normal standards for serum proteins adopted by various writers, particularly with respect to the normal range. These differences are due mainly to the variety of methods used, and some writers have failed to describe their methods in detail. The standards which we have adopted are essentially those of Bruck-

man, D Esopo and Peters,<sup>4</sup> whose values are almost identical with those we have obtained in fifteen normal subjects (members of the staff and students) The standards are as follows average values, total protein 7.30 per cent and albumin 5.00 per cent, globulin 2.3 per cent, normal range, total protein from 6.5 to 8.5 per cent, albumin from 4.2 to 5.7 per cent and globulin from 1.3 to 3.0 per cent For the purpose of comparison with the present series the serum proteins of twenty-one patients without edema, who are representative of the group from which our patients with edema are drawn, are shown in table 1

The results of the initial determinations of serum protein in the thirty-one cases are given in table 2 As has been stated, these determi-

TABLE 1—*The Serum Protein and Calculated Colloid Osmotic Pressure, Control Determinations in Twenty-One Patients Without Edema*

Name	Serum Protein				Calculated Colloid Osmotic Pressure	Diagnosis
	Total Protein	Albu min	Globu lin	Albumin/ Globulin Ratio		
L T	7.40	4.97	2.43	2.04	42.21	Syphilis, obesity
M T	7.26	4.87	2.39	2.04	41.38	Pellagra (?)
M H	7.92	6.15	1.77	3.47	49.82	Syphilis, obesity
C H	6.95	4.72	2.30	2.05	40.07	Hernia
L H	7.02	4.88	2.14	2.28	40.97	?
W H	6.79	4.91	1.88	2.61	40.69	Pellagra
N S	7.28	4.95	2.33	2.12	41.87	Recurrent pellagra
B A	7.09	4.30	2.79	1.54	37.86	Obesity
M T	7.47	5.35	2.12	2.52	44.47	Malnutrition
A B	7.75	5.48	2.27	2.41	45.75	Psychoneurosis
T J	7.83	4.73	3.10	1.52	41.71	Syphilis
T W	7.65	5.23	2.42	2.16	44.15	Hemorrhoids
P F	6.73	4.62	2.11	2.19	38.95	Toxic neuritis, diphtheritic (old)
I O	7.69	5.14	2.55	2.01	43.73	Nursing mother
J W	7.30	5.05	2.25	2.24	42.46	Pellagra
P H	7.87	4.44	3.43	1.29	40.17	Pellagra
M L	7.64	5.43	2.21	2.45	45.25	Albuminuria (slight)
L T	7.50	5.16	2.34	2.20	43.47	Pellagra
C H	7.62	4.92	2.70	1.96	41.97	Hypertrophy of prostate
J J	7.66	4.46	3.20	1.39	39.87	Constitutional inferiority
M H	7.29	5.02	2.09	2.40	41.93	Undernutrition (?)
Average	7.41	4.98	2.41	2.13	42.25	

nations were often made some days after the patients were first seen and frequently at a time when the edema was subsiding In the first three cases the total protein alone was determined, but they have been included in the series because they were among the first in which the condition was recognized and were typical examples of the disease, which was subsequently studied in greater detail

The total proteins varied but little from the normal, in most of the cases Though below the average normal<sup>5</sup> in twenty-two of the cases,

4 Bruckman, F S D'Esopo, L M and Peters J P The Plasma Protein in Relation to Blood Hydration IV Malnutrition and the Serum Proteins, J Clin Investigation 8 577, 1930 Although the principal title of this paper refers to plasma proteins it should be noted that the subtitle refers to serum protein and that serum was used in the determinations

5 Comparison with the average normal is of relatively little importance, comparison with the normal range is much more significant

values below the lower range of normal were found in but five and amounts less than 60 per cent in only three. The albumin fraction showed more significant changes. The individual values ranged from 1.72 to 4.97 per cent, with an average of 3.95 per cent, which is below the lower limit of normal. More significantly, the individual determinations were at or below the lower limit of normal in sixteen (59 per

TABLE 2—Initial Serum Protein Determinations in Thirty-One Patients with Edema \*

Case	Date	Edema†	Serum Protein				Calcu- lated Colloid Osmotic Pressure	Comment
			Total Protein	Albu- min	Glob- ulin	Albumin/ Globulin Ratio		
1929								
1	June 18	+	8.00					
2	July 19	+	7.50					
3	July 10	+	7.20					
4	July 23	+	7.00					
1930								
5	April 5	+	7.30	2.95	4.35	0.67	30.72	
6	April 22	+	6.20	3.05	3.15	0.96	29.13	
7	May 14	+	6.70	3.90	2.80	1.40	34.87	
8	July 16	+	7.30	3.90	3.40	1.14	36.03	
9	July 23	+	7.50	3.00	4.50	0.66	31.39	
10	July 25	+	6.51	3.71	2.80	1.32	33.44	
11	July 31	+	6.50	3.90	2.60	1.50	34.47	
12	Oct. 2	+	7.87	4.81	3.06	1.57	42.23	Edema disappearing
13	Nov. 19	0	6.97	4.52	2.45	1.84	38.85	
14	Dec. 15	?	6.46	4.28	2.18	1.96	36.55	
1931								
15	March 4	+	6.61	4.09	2.52	1.59	35.74	
16	March 9	+	7.91	4.31	3.60	1.28	39.51	Observed later with edema and lowered albumin
17	March 18	+	5.35	3.62	1.73	2.09	30.67	
18	March 25	+	6.50	3.94	2.56	1.53	33.10	
19	April 13	+	5.96	1.72	4.24	0.40	21.24	
20	April 23	+	5.94	3.19	2.75	1.16	29.40	
21	April 29	+	6.08	3.83	2.25	1.21	35.02	
22	April 29	+	6.83	3.89	2.94	1.32	35.07	
23	May 29	0	7.12	4.68	2.44	1.91	40.04	Edema previously
24	June 9	0	7.07	4.90	2.16	2.26	41.15	Edema previously
25	June 29	0	7.44	4.57	2.87	1.62	40.05	Edema previously
26	June 23	?	7.53	4.94	2.59	1.90	42.25	Edema off and on for 3 years, disappearing
27	July 7	+	7.23	3.87	3.36	1.15	35.73	
28	July 8	+	7.65	4.97	2.68	1.85	42.70	No edema 1 week later
29	July 23	+	6.75	4.47	2.28	1.93	38.14	Edema disappearing
30	July 29	+	6.69	4.50	2.19	2.05	38.20	Edema disappearing
31	July 29	+	6.93	4.14	2.79	1.48	36.64	Edema of face only

\* The clinical data on these subjects are given in the preceding paper.<sup>1</sup>

† No attempt was made to record the amount of edema at the time these determinations were made.

‡ In the statistical treatment of these data the cases marked ? have been considered to be without edema.

cent) of the cases. In sharp contrast to the albumin, the globulin was above normal average in all but five cases, and in nine cases was above the upper limit of normal. Values below the normal lower limit were not found in a single case. The albumin-globulin ratio, while less significant than the actual amounts of the two fractions, is of some interest in view of the strong tendency toward an increase in globulin in this series. Low ratios were frequent, the average being well below the average normal, while individual ratios below the lower normal were

TABLE 3—Repeated Determinations of Serum Proteins in Patients with Edema

Case	Date	Edema*	Serum Protein				Calculated Colloid Osmotic Pressure	Comment
			Total Protein	Albumin	Globulin	Albumin/Globulin Ratio		
3	1929 July 7	+	7.2					7/10 high protein diet with disappearance of edema in one month, hemoglobin increased
	1931 July 3	+	7.07	4.36	2.71	1.61	38.15	Return of edema, loss of weight
	Aug. 10	±	6.90	4.35	2.64	1.65	37.95	Edema in evenings
	Aug. 17	±	6.91	4.27	2.64	1.62	37.35	Diet unsatisfactory
5	1930 April 5	+	7.30	2.95	4.35	0.68	30.72	Brewers' yeast 15 Gm daily
	May 30	±	7.48	3.60	3.88	0.93	34.71	
	June 9	±	9.60	4.60	5.00	0.92	44.43	High protein diet
	June 19	+	9.60	3.50	6.10	0.57	38.29	High protein diet again advised
	July 7	0	8.50	2.80	5.70	0.49	32.23	
	July 21	0	7.70	4.10	3.60	1.14	37.93	
	Aug. 25	0	7.30	5.00	2.30	2.17	42.19	
	Oct. 13	0	7.85	4.68	3.17	1.48	41.47	
	Dec. 8	0	8.30	4.82	3.48	1.39	43.33	
	April 22	++	6.20	3.05	3.15	0.97	29.13	Increased protein (milk) ordered
7	May 13	+	8.20	2.95	5.25	0.56	32.48	Bitter tonic
	May 28	+	6.70	3.79	2.91	1.30	34.25	
	May 14	+	6.70	3.90	2.80	1.39	34.41	Brewers' yeast, 15 Gm daily
	May 21	+	8.15	2.65	5.50	0.48	30.71	High protein diet advised
	June 10	0	7.70	4.10	3.60	1.13	37.93	
	Oct. 13	0	7.21	4.62	2.59	1.78	39.88	
	Nov. 12	?	6.62	4.39	2.23	1.97	37.45	
	1931 March 20	±	6.61	4.39	2.22	1.98	37.43	
	Aug. 12	+	7.11	4.68	2.43	1.92	40.03	No edema 4 weeks later
	1930 July 23	+++	7.50	3.00	4.50	0.67	31.40	Brewers' yeast (15 Gm daily) for 1 week, then high protein diet added
13	Aug. 19	++	6.50	3.80	2.70	1.41	33.92	Edema present before and after this examination absent in May, 1931
	Oct. 1	?	8.01	5.25	2.76	1.90	44.97	
	Nov. 19	?	6.97	4.52	2.45	1.84	38.86	Edema returned
	1931 July 6	+	7.09	4.10	2.99	1.37	36.74	Marked diuresis and loss of edema 2 days before
	July 13	+	7.46	4.61	2.85	1.62	40.32	Diet probably unsatisfactory
	July 20	+	6.99	4.34	2.65	1.64	37.89	
	Aug. 17	+	7.34	4.46	2.88	1.55	39.25	Diuresis day before, bitter tonic
	March 20	+	7.80	3.70	4.10	0.77	35.89	
	March 25	+	6.50	3.94	2.56	1.54	34.70	
	April 6	0	6.53	4.06	2.52	1.61	35.52	
18	April 13	0	6.00	3.97	2.03	1.96	32.06	Gain of 2 Kg. since admission on 4/6/31 in spite of digitalization
	April 13	++++	5.96	1.72	4.24	0.40	21.97	
	April 27	++	6.63	3.53	3.10	1.14	32.67	Brewers' yeast, 15 Gm daily, since 4/21/31, loss of 2.8 Kg.
	May 11	+	6.33	3.37	2.96	1.29	32.30	Gain of 1.3 Kg., high protein diet
	May 18	±	6.74	3.64	3.10	1.17	33.50	Loss of 1.3 Kg.
	May 25	±	7.07	3.87	3.20	1.21	35.42	
	July 6	0	6.83	3.91	2.92	1.34	35.17	Weight constant
	July 27	0	8.94	4.49	4.45	1.01	42.53	Loss of 1.6 Kg.
	Aug. 17	+	6.94	3.71	3.23	1.15	34.27	Diet probably unsatisfactory
	Aug. 31	±	7.04	3.81	3.23	1.18	35.03	Gained 1.8 Kg.
21	Sept. 14	+	6.98	3.82	3.16	1.21	34.96	Slight loss of weight
	April 29	+	6.98	3.83	3.15	1.22	35.02	Gain of 7.3 Kg. in past eight weeks
	May 20	+	7.18	4.03	3.15	1.28	36.53	High protein diet begun 5/13/31

\* In the statistical use of these data the edema was considered absent in the cases marked ? and present in those marked ±

found in thirteen. In only one case was the ratio as high as the average normal.

The presence or absence of edema is recorded with the serum protein values in table 2, but for the purpose of presenting the relation of the edema to the serum proteins the results of the initial determinations have been grouped with the results of repeated determinations made in eleven of the cases (tables 3, 4 and 5). The inclusion of cases without edema in table 2 is due to the fact that some patients who had edema when first seen were free from edema when the serum protein was determined. Thus in four cases (cases 13, 23, 24 and 25) edema was

TABLE 4—*Nitrogen Metabolism, Serum Protein, Body Weight and Edema in Case 16*

Date, 1931	Nitrogen*				Serum Protein		Nonprotein		Wt., Kg.	Edema	Comment
	Intake, Gm.	Output	Urine, Gm.	Feces, Gm.	Total, per Cent	Albu min, per Cent	Glob ulin, per Cent	Nitro gen, per 100 Cc.			
March 9†					7.91	4.31	3.60	27	81.6	++++	
March 16									78.8	++	Admission to hospital low protein diet†
March 17	7.29	8.98	7.24	1.74	7.72	4.35	3.37	27	77.2	+	
March 18	6.31	8.62	7.65	0.97					77.0	±	
March 19	6.57	8.38	7.31	1.07					76.6	+	
March 20	6.50	8.31	7.31	1.00					77.0	++	
March 21	12.41	10.40	9.15	1.25	7.43	4.16	3.27	38	76.8	++	High protein diet begun
March 22	13.22	10.53	9.50	1.03					77.6	+	
March 23	13.78	13.82	12.40#	1.42					77.0	+	
March 24	14.14	11.72	10.87	0.85	7.30	3.91	3.39	34	76.5	+	
March 25	14.61	11.26	9.28	1.98					76.5	±	
March 26					7.48	4.16	3.32	24	76.8	±	
March 30†					7.36	4.18	3.18	24	78.3	±	Discharged from hospital
April 6†					7.12	4.02	3.10	25	77.8	±	

\* Actual daily determinations

† Observed in outpatient department

‡ All diets in the hospital were planned to contain a minimum protective amount of vitamins. Water was allowed ad libitum, and the sodium chloride intake was kept constant at about 5 Gm.

# This inconsistent value is unexplained and may be an error

absent at the time of the initial determination of serum protein and the albumin was within normal limits. Case 13 on subsequent observation showed edema and a low serum albumin. In five cases (cases 12, 16, 28, 29 and 30) edema was present when the albumin was at or above the lower limit of normal. In cases 12, 28, 29 and 30, the edema had disappeared within a week after the determinations were made, and was probably disappearing at the time of the examination. Case 16 subsequently showed edema and serum albumin below normal. In case 27, edema was questionably present with an albumin content of 4.94 per cent. In this case the edema, which had been present intermittently for years, was present before the determination of serum protein was made, but was absent later and was probably disappearing when the blood was studied.

Repeated determinations of the serum protein over periods of from three weeks to more than two years were made in eleven of the cases. The serum protein values under varying conditions of diet and treatment and their relation to the presence or absence of edema are pre-

TABLE 5—*Nitrogen Metabolism, Serum Protein, Body Weight and Edema in Case 17*

Date, 1931	Nitrogen*				Serum Protein			Nonpro	Wt ,	Edema	Comment
	Intake, Gm	Output			Total, per Cent	Albu min, per Cent	Glob- ulin, per Cent	tein Nitro gen, Mg per 100 Cc			
March 18†					5.35	3.62	1.73	35	56.7	++++	
March 26									50.9	++++	Admitted to hospital low protein diet‡
March 28}	5.66	5.96	4.77	1.09	6.52	3.77	2.75	30	49.3	++++	
March 29}	5.66	5.96	4.77	1.09					48.6	++++	
March 30}	5.66	5.96	4.77	1.09	6.40	3.83	2.57	30	47.5	+++	
March 31}	5.66	5.96	4.77	1.09					47.0	++	
April 1									47.6	++	Low protein diet continued
April 2								34	47.0	++	
April 3}	5.66	7.02	6.28	0.74					46.9	++	Brewers' yeast, 15 Gm daily
April 4}	5.66	7.02	6.28	0.74	7.07	4.35	2.72	30	46.6	+	
April 5}	5.66	7.02	6.28	0.74					46.7		
April 6									46.4	+	Low protein diet without yeast
April 7									46.4	±	
April 8}	14.24	10.70	9.38	1.32				30	46.0	±	High protein diet begun
April 9}	14.24	10.70	9.38	1.32					46.3		
April 10}	14.24	10.70	9.38	1.32					46.4	±	
April 11}	12.13	11.49	10.29	1.29	7.47	4.75	2.72	33	46.3		
April 12}	12.13	11.49	10.29	1.29					46.2	±	
April 13}	12.77	11.67	10.12	1.55					46.4	+	
April 14}	12.77	11.67	10.12	1.55	7.36	4.53	2.83	33	46.8	++	
April 15}	12.22	11.15	9.74	1.42					46.7	+	
April 16}	12.22	11.15	9.74	1.42					46.6	±	
April 18					7.44	4.57	2.87	32	46.0	±	Discharged from hospital
April 27					7.43	4.68	2.75	30	48.4	0	
August 5					7.53	5.07	2.46	20.6		0	

\* Average daily intake and output for the periods inclosed in brackets. In the first and last periods daily determinations were made.

† Observed in the outpatient department.

‡ All diets in the hospital were planned to contain a minimum protective amount of vitamins. Water was allowed ad libitum, and the sodium chloride intake was kept constant at about 5 Gm.

sented in tables 3, 4 and 5. In order to show the relation between the serum protein levels and the edema, the initial values in all of the cases have been grouped with those obtained on repeated examination, giving a total of eighty-three determinations of total proteins and seventy-nine determinations of the serum albumin and globulin.



The total serum proteins were determined eighty-three times in thirty-one patients. They were at or below the lower limit of normal in twelve examinations, with edema present at the time in ten. In sixty-seven instances the total protein was within the normal limits, with edema present in fifty. In four instances the total protein was higher than normal, with edema present in two. However, of the fifty instances in which edema was present with a normal or increased total protein, this level of total protein was the result of a globulin above the average normal in forty-seven, and above the upper limit of normal in twenty-six. In each of the four instances in which the total protein was abnormally high, the globulin was higher than normal.

Among the seventy-nine determinations of albumin, values at or below the lower normal were found in forty-five, with edema present at the time in thirty-nine and absent in six. The albumin was within the normal range in thirty-four instances, in nineteen of which edema was present. However, of the nineteen instances in which edema was present with a normal serum albumin, the latter was very near the lower limits of normal in ten. It should be emphasized that no attempt has been made to correlate the degree or the stage of edema (i.e., whether developing or disappearing) with the level of serum proteins.

The findings with respect to the globulin are in some respects the opposite of those in the case of albumin. In no instance was the globulin value found to be below the normal limits. Values within the normal range were found in forty-six analyses, with edema associated in thirty-one instances. The globulin was above the upper normal limit in thirty-three instances with an associated edema in twenty-seven.

The colloid osmotic pressure in these cases is of interest in view of the lack of correlation between the presence of edema and the amounts of total protein. They have been calculated by means of Govaerts' <sup>6</sup> factors (tables 2 and 3). <sup>7</sup> In thirty-nine instances the values were below those which Govaerts, using direct measurement, found in normal persons. Edema was associated with the lowered osmotic pressure in thirty-four. Normal values were found in forty, with edema present in twenty-five.

The relation between edema and the serum proteins is graphically represented in chart 1. It is seen that there is no correlation between the edema and the total proteins. There is some apparent relation in the case of albumin, although owing to causes which will be discussed

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<sup>6</sup> Govaerts, P. Influence de la teneur du sérum en albumines et en globulines sur la pression osmotique des protéines et sur la formation des oedemes, *Bull Acad roy de méd de Belgique* 7 356, 1927.

<sup>7</sup> The colloid osmotic pressures calculated from the data in tables 4 and 5 are included.

later, it is not very close. In the case of globulin there is a tendency toward a relation the opposite of that with albumin, in that high values of globulin are often found associated with edema. A similar finding was noted by Bruckman, D'Esopo and Peters.<sup>4</sup> Correlation is better in the case of total colloid osmotic pressure than with total protein.

In the cases in which repeated observations were made, it will be observed that there was a tendency for the edema to lessen as the albumin rose and to disappear as the albumin reached normal levels. In a number of instances, however, edema persisted for some time after the albumin had reached normal. The reverse was also true, and in those cases in which the albumin gradually declined, edema occasionally

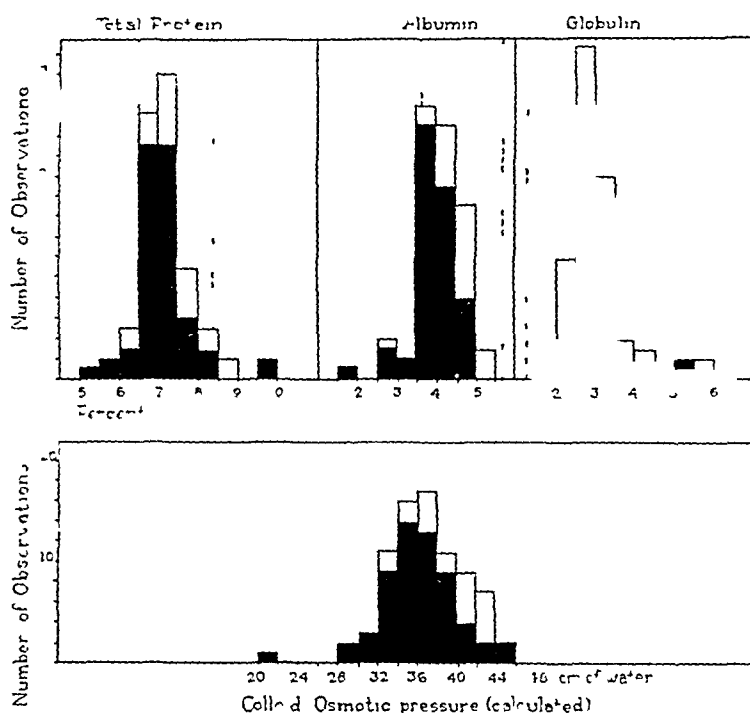


Chart 1—The relation of the serum proteins and of the calculated colloid osmotic pressures of the serum to the edema. The black areas indicate the presence of edema, the broken lines, the "normal" range.

failed to appear until some time after the albumin had sunk to a level below normal. In most of the cases the determinations were made too infrequently to determine accurately the time necessary for the albumin to return to normal. Usually there was some increase fairly soon after the diet was increased, but it was several weeks before the proteins reached their maximum (optimum?) levels. While this may have been partly due to a failure to take the diet recommended, the results in the cases of the two patients studied in the hospital and in Ling's<sup>8</sup> cases

<sup>8</sup> Ling, S. M. Change of Serum Proteins in Undernutrition, Chinese J. Physiol. 5:1, 1931.

suggest that a considerable time is necessary before the proteins reach their normal level in these cases

The globulin fluctuated rather widely from normal to abnormally high levels, but showed a tendency toward two distinct types of change. The first was a rise at the onset of improvement after treatment, which seemed to herald a rise in albumin. The second was a fall as the albumin increased.

The two patients who were admitted to the hospital for studies of nitrogen metabolism lost a great deal of weight and edema as soon as they were admitted and before they were placed on the diet with a high protein content. In one of them (case 17) there was a loss of 5.8 Kg between the time she was first seen in the outpatient department and the time that she returned for admission to the hospital. This loss of edema is not apparent in the tables because of the system of grading the edema which was used. In both cases the initial edema was much greater than the symbols indicate. The significance of this loss of edema is discussed later, but it may be pointed out that it is responsible for the lack of greater changes during the treatment in the hospital.

Both patients showed a slight negative nitrogen balance on the low protein diet which they were taking on admission and which was continued during the first few days in the hospital. In case 16, the patient was first placed on a diet containing approximately 41 Gm of protein, 137 Gm of carbohydrate, 76 Gm of fat and 1,396 calories. During a four days period on this diet the nitrogen intake was 26.67 Gm and the output 34.29 Gm. During the second period of five days she was given a diet of 92 Gm of protein, 169 Gm of carbohydrate, 77 Gm of fat and 1,800 calories. During this period she took in 68.16 Gm of nitrogen of which she retained 10.43 Gm. Actually the protein intake was somewhat less during the first two days and the retention was somewhat greater at the end than at the beginning of the period. Unfortunately it was impossible to keep her in the hospital longer. Except for the large initial loss of weight referred to, there was little change during this period. Four days after discharge she had gained 1.5 Kg and was practically free from edema. Five days later the weight had decreased slightly, but there is reason to believe that the diet was unsatisfactory. The serum albumin showed a slight drop during the period of the diet low in protein, and thereafter remained practically constant.

The second patient (case 17) was given, on admission, a diet of 35 Gm of protein, 153 Gm of carbohydrate, 46 Gm of fat and 1,166 calories, a somewhat larger amount of calories than she had been receiving prior to admission, and near her basal requirement. During the first period the nitrogen intake was 22.66 Gm and the output 23.85 Gm. During the second period the same diet was continued but brewers' yeast

(15 Gm daily) was added. The nitrogen intake during this three days period was 17 Gm and the output 21.07 Gm. After an interval of two days on the low protein diet without yeast she was given a diet consisting of 74 Gm of protein, 88 Gm of fat, 176 Gm of carbohydrate and 1,792 calories. The nitrogen intake during this nine days period was 116.96 Gm, of which she retained 16.22 Gm. However, the actual nitrogen intake was greater during the first part of the period, averaging nearly 90 Gm for the first three days. The edema, which was only slight after the initial loss of weight, gradually lessened and was practically absent on discharge. It should be remembered that the changes in weight in these experiments are the result of two opposite changes, the loss of edema and the improved nutrition, and that in a short period the changes in weight need not parallel the changes in edema. When seen in the outpatient department three days after discharge, the patient was without edema and had gained 2.7 Kg. The serum albumin rose slightly even before she was placed on the diet of high protein content, and was accompanied by a decrease in the edema. During the latter part of the period in the hospital the albumin was slightly below the amount found on April 11, and during this period the weight was stationary. The maximum amount of albumin was attained some time after discharge.

#### COMMENT

In general, the results of this study show that the edema in these cases was associated with a normal total protein, a normal or increased globulin and a slight to moderate reduction in the serum albumin. The last finding is the most important, the reduction, while not great, is believed to be significant, and the fact that the deviation from normal was small is consistent with the generally mild nature of the disease. Greater reductions in the serum albumin have been reported by other writers. Several factors are probably responsible for this difference between their results and ours. In some instances variations in methods and standards may be partly responsible. Much more important is the difference in the severity of the disease, the circumstances under which our studies were made, and their influence on the relation between the occurrence of edema and the level of the serum proteins. Lowered osmotic pressure caused by a reduction of serum protein is only one of the two principal factors thought at present to be concerned in the formation of this type of edema, and determines only a "tendency toward edema." If one accepts the hypothesis of Starling,<sup>9</sup> the occurrence or nonoccurrence of the edema depends primarily on the balance between colloid osmotic pressure and intracapillary pressure, edema is

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<sup>9</sup> Starling, E. H. On the Absorption of Fluids from the Connective Tissue Spaces, *J. Physiol.* **19**:312, 1895-1896.

the result of a disturbance in this balance. Other factors, such as "tissue pressure" and electrolyte and hydrogen ion concentration, are probably of secondary importance only, the latter through their influence on the Donnan equilibrium. An increase in capillary pressure can cause a filtration of water from the blood into the tissue spaces in the presence of normal amounts of protein.<sup>10</sup> Krogh, Landis and Turner<sup>11</sup> have recently shown that the erect human being is always near edema. Therefore, even a slight reduction in the serum protein below the lower limits of normal might result in the formation of edema, provided the other factors remain constant (normal).

All the patients studied were ambulatory patients more or less engaged in their usual activities. It is to be expected therefore, that edema would occur at higher concentrations of serum proteins than in patients who were studied in the hospital and whose activity was greatly restricted. Burger<sup>12</sup> has emphasized the influence of exercise in increasing the formation of edema in these cases. Furthermore, the amount of edema may be expected to parallel more or less closely the decrease in serum protein, and therefore the edema in most of these cases should be much less than in those patients whose serum proteins are greatly reduced, as was actually the case. On the other hand, because of the effect of recent muscular exercise<sup>13</sup> and standing position,<sup>14</sup> higher values for serum proteins may have been present temporarily at the time the blood was drawn.

The influence of physical activity is reflected in the absence of a sharp, critical level of serum albumin, such as has been described by Weech and Ling in "famine edema"<sup>15</sup> and by Moore and Van Slyke<sup>16</sup>

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10 Drury, A. N., and Jones, N. W. Observations upon the Rate at Which Edema Forms When the Veins of the Human Limb Are Congested, *Heart* **14** 55, 1927

11 Krogh, A., Landis, E. M., and Turner, A. H. The Movement of Fluid Through the Human Capillary Wall in Relation to the Venous Pressure and to the Colloid Osmotic Pressure of the Blood, *J. Clin. Investigation* **11** 63, 1932

12 Burger, M. Die Odemkrankheit, *Ergebn. d. inn. Med. u. Kinderh.* **18** 189, 1920

13 Rowe, A. H. The Effect of Muscular Work, Diet and Hemolysis on the Serum Proteins, *Arch. Int. Med.* **19** 499 (April) 1917

14 Thompson, W. O., Thompson, P. K., and Dailey, M. E. The Effect of Posture upon the Composition and Volume of the Blood in Man, *J. Clin. Investigation* **5** 573, 1928. Ni, T., and Rehberg, P. B. On the Influence of Posture on Kidney Function, *J. Physiol.* **71** 331, 1931

15 Weech, A. A., and Ling, S. M. Nutritional Edema. Observations on the Relation of the Serum Proteins to the Occurrence of Edema and to the Effect of Certain Inorganic Salts, *J. Clin. Investigation* **10** 869, 1931

16 Moore, N. S., and Van Slyke, D. D. The Relationship Between Plasma Specific Gravity, Plasma Protein Content and Edema in Nephritis, *J. Clin. Investigation* **8** 337, 1930

and by Peters and his associates<sup>17</sup> in cases of chronic renal edema. Because of the inability to measure and control the factors, other than the amounts of protein, concerned in the production of edema, a sharp critical level of the latter is not apparent in our cases. The failure to show a critical level of serum albumin is also partly due to the variations in serum globulin and to the "lag" in the formation or disappearance of edema with changes in the concentration of protein. As is shown in the tables, when a normal or nearly normal value for albumin was found in association with edema, it almost always occurred at a time when the edema was receding but had not entirely disappeared. In many cases the edema was absent a short time later. This lag in the edema will explain many of the discrepancies in the relation between the edema and the albumin concentrations. Although studies were not made in the case of ambulatory patients, there is no reason to believe that intracapillary pressure in these patients was higher than in normal persons under similar conditions. The venous pressure was determined by direct measurement in the two patients who were admitted to the hospital (cases 16 and 17). In both instances normal values, 10 and 6 cm of water respectively, were found. These pressures are, of course, lower than those that existed during periods of normal activity.

The total colloid osmotic pressure of the serum is of interest in view of the occurrence of edema with normal total proteins and only slight to moderate reductions in serum albumin. The calculated values in our patients are in general slightly below the calculated normal average and also slightly below the values that Govaerts<sup>6</sup> found by direct measurement in normal persons. As would be expected, for the reasons already discussed, they are considerably higher than those which have been reported in other types of edema.<sup>18</sup> Fahr, Kerhof and Conklin<sup>19</sup> have recently reported colloid osmotic pressures in normal subjects, determined by direct measurement, considerably below those found by Govaerts. This is of little significance in the present discussion, however, since our figures were obtained by calculation using Govaerts'

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17 Peters, J. P., Bruckman, F. S., Eisenman, A. J., Held, P. N., and Wakeman, A. M. The Plasma Proteins in Relation to Blood Hydration. VI. Serum Proteins in Nephritic Edema, *J. Clin. Investigation* **10** 941, 1931.

18 Govaerts<sup>6</sup> Schade, H., and Claussen, F. Die onkotische Druck des Blutplasmas und die Entstehung der renalbedingten Odeme, *Ztschr. f. klin. Med.* **100** 363, 1924. Mayrs, E. B. The Functional Pathology of Nephritis, *Quart. J. Med.* **19** 273 (April) 1926. Fahr, Z., Kerhof, A., and Conklin, Claire. Osmotic Pressure of Plasma Proteins in Nephritis, *Proc. Soc. Exper. Biol. & Med.* **28** 720, 1931.

19 Fahr, Z., Kerhof, A., and Conklin, Claire. Normal Osmotic Pressure of the Plasma Proteins in Man, *Proc. Soc. Exper. Biol. & Med.* **28** 718, 1931.

factors and would be correspondingly lowered if the latter were shown to be too high

Certain secondary factors, particularly the intermittent and chronic nature of the disease and the intake of water and salt, may have influenced the development of edema in our cases. Edema develops more easily following an initial attack, possibly because of a lessened "tissue pressure" owing to a loss of tissue elasticity. Many of the patients had had previous attacks and several had been edematous at intervals for years. Variations in salt and water intake are known to have a considerable influence on this type of edema. Peters and his collaborators<sup>17</sup> have shown that in nephritic edema associated with lowered proteins, variations in salt and water intake have a marked influence on the edema unless the proteins are at a very low level. With an exception in the case of the two patients who were the subjects of the studies of nitrogen balance in which the salt intake was controlled, no attempt was made to control the salt and water intake in our cases.

The possibility that an injury to the capillary endothelium occurred as a result of continued dietary insufficiency has been considered. Edema due to this cause should be characterized by an edema fluid with a protein content similar to that of the blood plasma. Unfortunately the edema was too slight in most of the cases to permit obtaining samples of edema fluid free from contamination with blood. In one patient (case 17) a small amount of edema fluid was obtained which showed a high concentration of protein, but slight contamination with blood rendered the result unreliable. Edema fluid obtained from a case of sporadic nutritional edema, not included in this series, contained 0.6 per cent protein, of which 0.4 per cent was albumin.

An increase in the serum globulin occurred too often and was too great to be considered only coincidental. Neither is there any evidence that the high globulin content was the result of infection. It is possible that the high values are partly due to the preponderance of women in our series since the findings of Bruckman, D'Esopo and Peters<sup>4</sup> suggest that women have a somewhat higher globulin than men. A similar increase in globulin, however, was found by Ling<sup>8</sup> and Weech and Ling,<sup>15</sup> who ascribe to it a minor rôle in restricting the formation of edema in their cases. These authors noted, in particular, a tendency for the globulin value to rise shortly after the institution of a curative diet and before an increase in albumin occurred. A similar change was found in our cases together with a tendency for the globulin content to fall as the albumin rose. Leiter,<sup>20</sup> Barker and

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20 Leiter, L. Experimental Nephritic Edema, *Arch Int Med* **48** 1 (July) 1931

Kirk<sup>21</sup> and Shelburne and Egloff<sup>22</sup> found a relative or absolute increase in globulin in dogs with an experimental edema produced by plasmapheresis, and Leiter noted that the globulin increased much more quickly than the albumin when plasmapheresis was discontinued. Bruckman, D'Esopo and Peters<sup>4</sup> expressed the belief that the increase in globulin observed by them is coincidental, the result of such factors as syphilis or other infections, and stated that the changes in globulin cannot be correlated with the occurrence of edema. While this is undoubtedly true, in the sense that no relation of cause and effect between a lowered globulin content and edema can be demonstrated, our results show a distinct tendency toward an increased globulin with a lowered albumin content (chart 2) and a greater frequency of edema

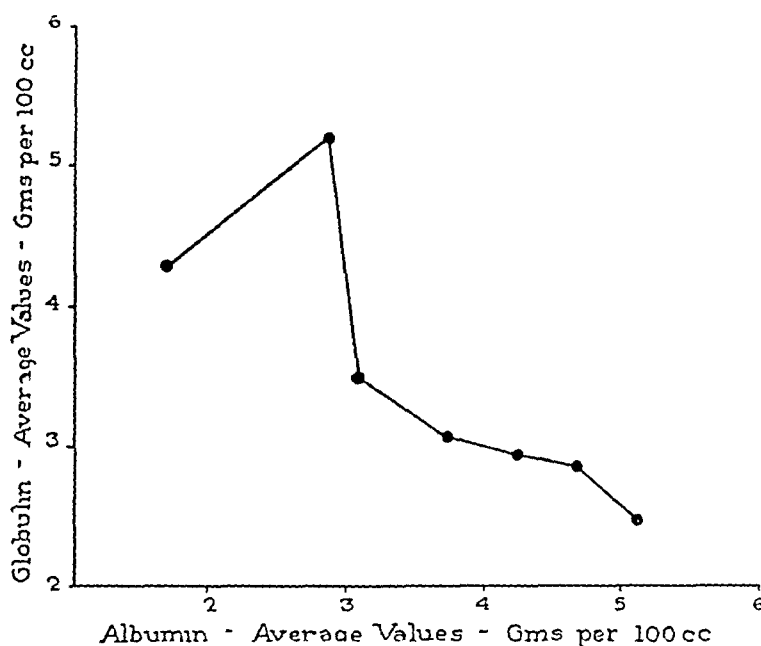


Chart 2—In this chart the average values for each group of albumin determinations at intervals of 0.5 per cent (1.50-1.99, 2.00-2.49, etc.) have been determined, and the average values for the corresponding globulin determinations are plotted against them. The first point represents a single determination only. The tendency for the globulin to fall as the albumin values rise is evident.

among the cases with increased globulin. Our results and those of others suggest strongly that the increase in globulin in these cases is in the nature of a compensatory response which, however, often fails to prevent the occurrence of edema. Salvesen's case<sup>23</sup> has frequently

21 Barker, M. H., and Kirk, E. J. Experimental Edema (Nephrosis) in Dogs in Relation to Edema of Renal Origin in Patients, *Arch. Int. Med.* **45**: 319 (March) 1930.

22 Shelburne, S. A., and Egloff, W. C. Experimental Edema, *Arch. Int. Med.* **48**: 51 (July) 1931.

23 Salvesen, H. A. Hyperproteinemia in a Case of Nephrosis, *Acta med. Scandinav.* **45**: 152, 1926.



been cited to show that globulin, though its osmotic pressure is lower, may, when present in sufficient concentration, prevent the formation of edema even in the presence of a very low albumin content. In our cases the increase in globulin was rarely sufficient to prevent entirely the formation of edema, but in several instances probably prevented the formation of much greater amounts. Weech and Ling found that when the globulin content was low, edema was almost always present and the albumin invariably deficient. The edema was considerably greater in their patients than in ours, and the protein concentrations were correspondingly lower. On the other hand, increases in globulin were greater and more frequent in our series. Although it is probable that the same cause is responsible for a globulin deficit as for albumin, it may be that the two fractions are unequally affected. It is suggested that the increase in globulin, though compensatory, is only possible in the milder or earlier stages of the disease or during the earlier stages of recovery.

The feeding of a diet of higher protein content was in a general way associated with an increase in the serum proteins and a lessening or disappearance of the edema, but the serum albumin did not rise to normal values for relatively long periods (six or eight weeks). This may have been due in part to an intake of protein lower than was advised. However, in Ling's patients on a diet of high protein content in the hospital, the serum albumin failed to reach normal over even longer periods, though the edema disappeared earlier. In contrast to Ling's findings the edema in our cases tended to persist until the albumin was well up to normal values. The difference between these two classes of patients and the influence of the factors discussed in relation to the edema and protein values are well illustrated by the two subjects of the studies of nitrogen balance. When confined to bed, with a resulting restriction of activity, both patients promptly lost the greater part of their edema (2.7 and 3.6 Kg., respectively) without any significant change in the serum proteins. Neither of these patients showed any marked gain in serum protein during her stay in the hospital in spite of a retention of nitrogen when placed on a diet of high protein content. The time, however, was much shorter than that necessary to raise the protein content to normal in the case of the outpatients. One patient was subsequently found to have a normal serum protein value and a complete loss of edema. The other could not be followed over a long enough period. The failure of the serum proteins to return to normal in relatively long periods in spite of a high protein intake, is interesting. It is probable, since the serum proteins continued to increase for a long time, that nitrogen retention continued during the entire period, though neither our studies nor those

of others have been continued sufficiently long to demonstrate this. These observations suggest that in cases of nutritional edema the depleted nitrogen stores of the tissue are replenished before the serum proteins are greatly increased. On the other hand, in normal dogs made edematous by removing blood plasma (plasmapheresis), restoration of the serum protein may occur rather rapidly when an increased protein diet is fed,<sup>22</sup> and the possibility of some interference with regeneration of the serum protein in patients subjected to long-continued malnutrition must be considered. A few of the patients were given brewers' yeast for varying periods without a change in diet to determine whether an increased supply of vitamin B would influence the edema. In one or two of them there was a prompt rise in serum albumin. The protein content of the yeast was insufficient to account for the increase. The observations were too few and incomplete, however, to make the results more than slightly suggestive.

#### SUMMARY

Initial determinations of the serum proteins in thirty-one patients with nutritional edema and repeated observations in eleven of them, amounting in all to eighty-three determinations of total proteins and seventy-nine of serum albumin and globulin, are reported. In general, the total proteins were found to be normal, the serum albumin slightly or moderately reduced and the globulin normal or increased. Calculated colloid osmotic pressures were slightly or moderately below normal in the majority of patients with edema. When the protein in the diet was increased, the albumin tended to rise gradually, accompanied by a disappearance of the edema. However, this association was not exact, owing partly to a lag in the disappearance of the edema and partly perhaps to the influence of factors as yet not fully understood. Among the outpatients, irregularities of diet and infrequent observations may account for some of the discrepancies. In two cases, studies of nitrogen balance showed a retention of nitrogen on an increased protein intake. In one of these patients who was followed over a sufficient period there was an eventual rise in serum albumin to normal and a disappearance of the edema. The significance of these findings in relation to the edema is discussed.

# DETECTION OF THE MURMUR OF ACUTE PERICARDITIS

## DESCRIPTION OF A NEW CLINICAL PROCEDURE

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Until the introduction of auscultation dry pericarditis was a disease only discovered on the post mortem table. The only evidence we have of its presence is the characteristic superficial to and fro murmur produced by movements of the heart. Its discovery is usually accidental and made when the heart is examined as a routine. There is no distinctive sign associated with it and in marked contrast to pleurisy it is essentially a painless complaint.

*See James Mackenzie,<sup>1</sup> 1925*

The foregoing quotation reflects quite accurately the general attitude of physicians to the diagnosis of acute fibrinous pericarditis. Similar paragraphs may be found in most textbooks. In the most recent of the good monographs on heart disease, Dr Paul D White<sup>2a</sup> presented statistics which amply prove the opinions of Sir James Mackenzie. Dr White said, "The characteristic sign of acute pericarditis, often found at some stage of the disease, is the friction rub, but in many cases (over 75 per cent) it is absent or escapes notice (Cabot 1926 a friction rub was heard in only 40, or 21 per cent of 186 cases of acute pericarditis)." It is indeed a common experience of clinicians to fail in detecting a pericardial friction murmur in cases which present an etiologic factor or symptoms suggesting pericarditis.

The salient features of the evolution of knowledge about the pericardial friction murmur offer some evidence which tends to explain these experiences. In a chapter devoted to the differential diagnosis of cardiac murmurs Laennec<sup>3a</sup> spoke of a *cii de ciii* sound which he said he at one time suspected of being a sign of pericarditis, but which he attributed to certain forms of exudative bronchitis. Laennec seems to have missed entirely the significance of this murmur, for although

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1 Mackenzie, James. Diseases of the Heart, New York, Oxford University Press, 1925

2 White, P D (a) Heart Disease, New York, The Macmillan Company, 1931, p 509, (b) pp 509 and 510

3 Laennec, R T H (a) *Traité de l'auscultation mediate et des maladies des poumons et du cœur*, ed 4, Paris, Masson & Cie, 1837, vol 3, pp 105 and 106, (b) p 375

Collin<sup>4</sup> described its association with three cases of pericarditis in 1824, no reference to these observations is found in the 1826 edition of Laennec's book. This may in part be due to the fact that both Laennec<sup>3b</sup> and his master, Corvisart,<sup>5</sup> taught that it was almost impossible to make a clinical diagnosis of pericarditis, and in part, also, to the uncertain tone in which Collin wrote of his observations. Of the three cases, he himself had studied only one. This patient presented a murmur analogous to the creaking (*claquement*) of new leather, which persisted for six days before signs of pericardial effusion developed, the patient died, but no autopsy was performed. The other two cases were described to Collin by Devilliers, a junior intern of Saint Antoine Hospital. Devilliers performed an autopsy in the second of these cases and found fibrinous pericarditis. From these observations Collin concluded that "Perhaps this murmur may be a constant sign of pericarditis before the development of pericardial serous effusion," and he attributed the murmur to pathologic dryness of the pericardium, which, moreover, he postulated as a characteristic of the initial stage of pericarditis. The first thorough clinicopathologic study of the auscultatory signs of pericarditis was made by William Stokes<sup>6</sup> (1834). This eminent clinician drew attention to the relative frequency of pericarditis, to the great variability in the quality and loudness of the friction murmur and to its frequent resemblance to other cardiac murmurs, he stated that though the murmur described by Collin is characteristic of pericarditis, it is the rarest of all the pericardial friction murmurs. In his book "The Diseases of the Heart"<sup>7</sup> (1854), Stokes alluded to the effect which posturing the patient has on the appearance and disappearance of the friction murmur, a fact first observed by Corrigan<sup>8</sup> (1842).

Because of the close resemblance between the protean forms of the pericardial friction murmur and endocardial and so-called functional murmurs, Stokes' observations have been ignored, and clinicians are inclined to depend on the discovery of the creaking, leathery, to-and-fro murmur for the diagnosis of pericarditis. Moreover, although Corrigan's observation suggests a method of eliciting the friction murmur, this procedure of changing the patient's posture is not reliable, since endocardial murmurs also vary with changes in the patient's posture.

4 Collin, V. Des diverses methodes d'exploration de la poitrine, Paris, J. B. Baillière, 1824.

5 Corvisart, J. N. Essai sur les maladies et les lésions organiques du cœur et des gros vaisseaux, in Alibert, Bayle and others. Encyclopédie des sciences médicales, Paris, 1818, p. 1.

6 Stokes, William. Dublin J. M. Sc. 4 29, 1833-1834.

7 Stokes, William. The Diseases of the Heart and Aorta, Philadelphia, Lindsay and Blakiston, 1854, p. 20.

8 Corrigan, D. J. Proc. Path. Soc. Dublin, December, 1842.

The great frequency of cardiac murmurs of the endocardial type in rheumatic diseases, such as rheumatic fever and chorea, in cases of pneumonia and in septicemias and uremic states, militates against the discovery of pericarditis in such cases when the friction sound resembles an endocardial murmur. The lack of a satisfactory method of differentiating pericardial from endocardial murmurs has naturally led clinicians to consider all these murmurs as endocardial. Thus, one may conclude that the clinical diagnosis of fibrinous pericarditis is usually made only when the creaking, leathery, to-and-fro murmur arrests the attention of the observer.

My interest in the problem of eliciting the pericardial friction murmur, when it is not heard during an ordinary careful examination of the heart, and of differentiating it from other cardiac murmurs was aroused by the observations made in the following case.

#### REPORT OF A CASE

*Observations Before Admission to Hospital*—A F, a boy, aged 15, on Feb 16, 1930, became rather acutely ill with pains in the abdomen as he got up in the morning, he had to return to bed after attempting to wash and dress. The abdominal pain persisted all day, and in the evening he vomited. During the next four days the abdominal discomfort continued as a rather bad ache with occasional severe exacerbations, and he was unable to retain any food, for he vomited soon after eating. He was able to retain water and orange juice. He was first observed by his physician, Dr B W Segal, on February 20, when a moderate degree of fever, 102 F, and some generalized abdominal tenderness were found. When first seen by me in consultation with Dr B W Segal on February 26, he still had the abdominal symptoms described, and, in addition, it was learned that deep breathing aggravated the abdominal pain and might cause vomiting, and that at times he had numbness or sensations of pins and needles in both hands and arms. On February 25, he began to notice some pain in the throat on swallowing and some pain in the left anterior part of the chest on taking a deep breath.

*Past History* The patient had had measles, German measles, pneumonia, influenza and occasional colds as a small child. Tonsillectomy was done when he was 8 years of age. At 13 he had rheumatic fever, when he was ill for three months in the Royal Victoria Hospital and rested in a convalescent home for one month, a year later he had a mild recurrence, with illness for only two weeks. He did not recall having had any sore throat since the tonsillectomy.

*Habits* The patient usually slept and ate well, the bowels were regular, there was no nocturia. He attended school from the age of 5 to 13, and since then, when not ill, had worked as a messenger.

*Family History* The mother had died of a disease which caused dyspnea, in 1925, the father and three other children were alive and well, one younger sister had died of heart disease.

*Physical Examination (February 26)* The patient was a well developed and well nourished boy of 15, with a rather sallow complexion, who did not appear to be acutely ill. The body temperature was 102.6 F. The throat was acutely inflamed, there was some mucopurulent exudate on the posterior pharyngeal wall. There were very small tonsillar tissue remains from the tonsillectomy. The breath-

ing was rather rapid, 40 per minute, and shallow. Percussion resonance over the left base was somewhat impaired, and a few moist crackles were heard during inspiration at the base of the left lung posteriorly, no other abnormal pulmonary signs could be detected. The abdomen was tender all over, but most acutely in both flanks, the liver was palpable  $1\frac{1}{2}$  inches (3.77 cm) below the right costal margin, no special area of rigidity of the abdominal wall could be defined. There was some tenderness in both costovertebral angles. The fundi presented somewhat engorged veins. No petechiae and no abnormalities of the skeletal muscles or joints could be detected.

Examination of the heart revealed the following. The apex impulse was 8 cm from the midsternal line and 2 cm to the left of the midclavicular line, a short presystolic thrill and a sharp systolic shock were felt at the apex, relative cardiac dullness was 2, 3.5, 6 and 8 cm from the midsternal line in the second to fifth left interspaces and 3, 3 and 4 cm in the second to fourth right interspaces. At the apex were heard a loud sharp first sound, a rather faint second sound and a decrescendo-crescendo diastolic murmur, the decrescendo phase was a short rumble which began a short time after the end of the second sound and faded completely, then after another brief interval the loud coarse crescendo phase began, and continued until it was interrupted by the loud sharp first sound. At the pulmonic area the first sound was short, dull and not loud, the second sound was loud and sharp and followed by a short diastolic "whiffy" murmur which began immediately after the end of the second sound, this murmur became louder as the stethoscope was moved downward along the left border of the sternum and was loudest and longest at the fourth space, where it occupied about half of the diastolic period and had a high-pitched blowing quality. At the aortic area and along the right border of the sternum the auscultatory signs were similar to those along the left border, but were less loud. No friction rub could be detected during ordinary auscultation, and it could not be elicited by a change in posture from the sitting to the recumbent positions, and vice versa. The blood pressure was 125 systolic and 60 diastolic, the heart rhythm was normal, and the rate was 100.

There was, of course, rheumatic heart disease, with mitral stenosis, aortic insufficiency, some left ventricular enlargement and apparently good cardiac function. However, no well defined cause for the symptoms and the fever could be determined, peritonitis, perhaps associated with acute appendicitis, recurrence of rheumatic fever or pneumonia, and pleurisy with referred abdominal pain were some of the possibilities to be considered. The patient was admitted to the Montreal General Hospital, in the medical service of Dr. A. H. Gordon.

*Observations Made in the Hospital*<sup>9</sup>—The salient features of the examination on admission (Feb. 27, 1930), made by the junior intern, were as follows: an acetone odor of breath, perhaps some impairment of percussion resonance and bronchial breathing over the right base in the axillary region, slight bulging of the chest over the precordium, relative cardiac dullness 12 cm from the midsternal line in the fifth left interspace, heart sounds loud at the apex, and "possibly a pericardial friction rub, heard best at the apex—this may be a mitral murmur. At base, second sound over aortic area is very sharp and distinct." There was tenderness and rigidity of the whole abdomen, most marked in the upper quadrants, and pain radiated into the loins. The liver was palpable 1 inch (2.5 cm) below the costal margin in the midclavicular line. Pressure on the

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<sup>9</sup> Dr. A. H. Gordon and colleagues of both hospitals permitted me to abstract and quote their notes.

abdomen caused discomfort in the lower left side of the chest. There was a slight icteric tinge over the face and the abdomen.

**Electrocardiogram** Taken on February 28. This showed sinus rhythm, with a rate of 100, a partial auriculoventricular block, P-R interval, 0.25 second, left axis deviation, with the P and T waves upright in all leads. The S-T interval was slightly above the base line in leads I and II. This record was considered to present evidence of active rheumatic myocarditis and relative enlargement of the left ventricle associated with aortic insufficiency, adherent pericardium or both.

**Urine** The specific gravity was 1.022, the urine contained no sugar, albumin or casts (acetone ++ only on first day, and then absent).

**Single X-Ray Plate of Chest** (February 28) "Cardiac diameters show marked increase throughout. No evidence of any fluid in the pleural cavities. On the

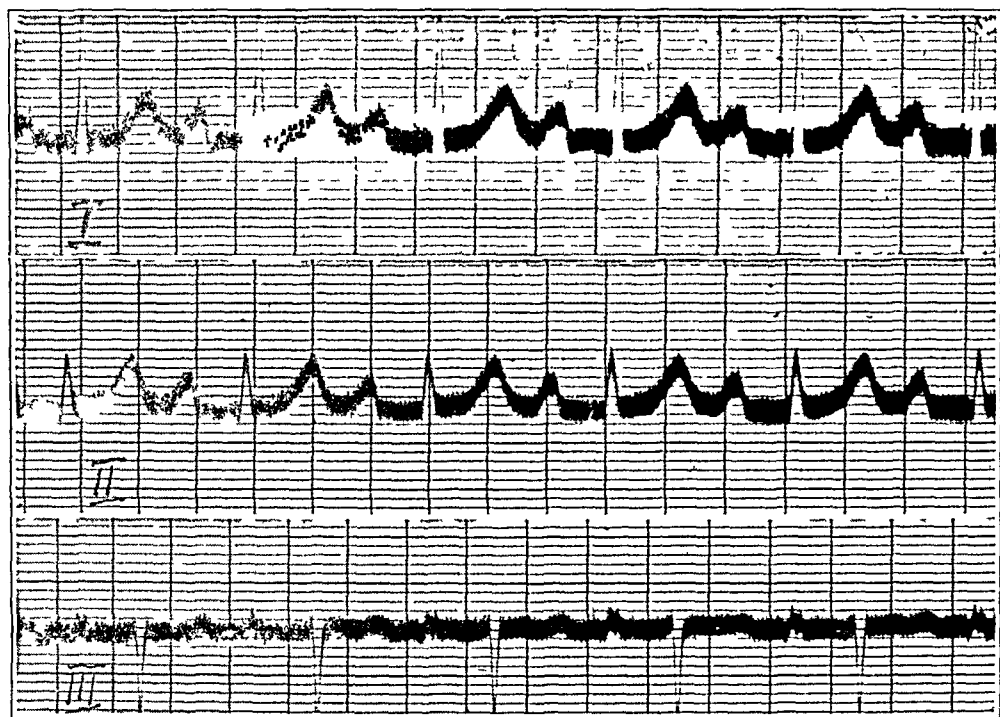


Fig 1—Electrocardiogram recorded on Feb 28, 1930, showing partial auriculoventricular block, P-R interval, 0.25 second, rate, 100, left axis deviation, S-T interval, slightly above baseline in leads I and II.

left side in the sixth and seventh interspaces, extending from the cardiac shadow out to the axillary line, there is what appears to be some increase in density which might represent a small pneumonic process."

**Examination of Blood** (February 28) A count showed red cells, 3,700,000, white cells, 23,800, hemoglobin, 70 per cent, polymorphonuclears 88 per cent, basophils, 2 per cent, lymphocytes, 8 per cent, monocytes, 2 per cent. The platelets seemed increased and clumped. Chemical analysis of the blood showed urea nitrogen, 13 mg, creatinine, 17 mg per hundred cubic centimeters, and sugar, 0.135 per cent.

**Extracts of Clinical Notes** Made by Dr. D. Mitchell, Senior House Officer, on March 1, in the Morning. The percussion note over the lungs was somewhat resonant except low in the left axillary region, where it was impaired, this had

been more pronounced the previous day. The breath sounds had been normal the previous day, but just at the outer border of cardiac dulness, there was a definite pleural friction, on this day this could not be heard. The relative cardiac dulness was 9 cm from the midsternal line in the fifth left interspace. A presystolic murmur was heard at the apex, no thrill was felt. No other murmurs were heard. The impression was rheumatic carditis, rheumatic pleurisy and decompensation.

Extracts of Clinical Notes by Dr. A. H. Gordon, on the Afternoon of March 1. The respirations were 36 per minute, the pulse rate, 96. There were a slight dulness of the percussion note and a slightly diminished loudness of the breath sounds over the base of the left lung. The heart was enlarged to the left, and auscultation at the apex revealed a canter rhythm of 3 beats, the first of which was the longest, no murmurs were heard. The abdomen was soft throughout, but tenderness was fairly diffuse and noticeably present in the right lower quadrant. The patient had coughed up a mass of blood-streaked mucopurulent sputum that did not resemble pneumonic sputum. The history of abdominal discomfort with the presence of definite tenderness was rather disturbing, but taken altogether the case suggested an atypical form of pneumonia.

A surgical opinion was requested, and on March 2, Dr. A. T. Bazin advised against immediate surgical intervention, although he could not rule out the possibility of acute appendicitis.

Clinical Notes by Dr. Gordon, March 3. "At apex there is a triple rhythm, a dash and two dots, with the dash systolic, and there is a short systolic murmur. At the base the first and second sounds are clear, immediately succeeding the second sound there is a soft rub, when this is followed downward it takes on a to-and-fro character, distinctly scratching in quality and not exactly coincident with the first or second sound. This is regarded as a pericardial friction rub."

Course. From February 27 to March 8, I failed to discover the pericardial friction murmur described, although the patient was observed at least once daily and occasionally two or three times. The auscultatory signs were consistently such as described when the patient was seen by me at his home. On March 8, during the usual attempts to elicit the friction murmur by changing the patient's posture, a loud to-and-fro *cui de cui* type of pericardial murmur was heard all over the sternum during the time occupied by about a dozen heart beats, then it disappeared, several repetitions of the postural changes failed to elicit the murmur again. These experiences led me to think of the pathologic anatomy in this case. Visualizing the serofibrinous exudate, with just sufficient serum to separate the two layers of the pericardium, it occurred to me that by shaking the body of the patient, the heart might be caused to swing, somewhat in pendulum fashion, and thus the two layers of pericardium might be brought into contact for at least a sufficiently long period to elicit the friction murmur. With the patient in the dorsal recumbent position and the observer's hands on the chest in the axillary regions, the patient was shaken from side to side about half a dozen times in rather quick succession, on listening over the sternum immediately after this procedure, the loud friction murmur was heard again for about ten seconds, after which it disappeared. The shaking was repeated about a dozen times, and each time the murmur was heard during from ten to thirty seconds. From March 8 until March 20, the friction murmur remained audible. On ordinary auscultation, before shaking, it was heard on three occasions during this time. However, it could be elicited almost invariably after one shaking procedure, although sometimes only after two or three. A more gentle and equally effective method is to place the patient in the right lateral recumbent posture and have him move toward the



dorsal and prone postures, back and forth, several times. This procedure lends itself well in cases of adults, particularly heavy persons. The murmur was usually of the typical creaking, leathery, rubbing kind, but wide variations in loudness and quality were observed. Sometimes the systolic phase was loud, whereas the diastolic was barely audible, or the to-and-fro murmur had a soft swishing quality, and the elements varied in duration. At times the friction murmur resembled a systolic or a diastolic intracardiac murmur, from which it was distinguished only by its absence before shaking the patient and its disappearance after a few moments or minutes.

The patient remained in the hospital during ten weeks. Only occasional fleeting pains in the joints and muscles occurred to suggest rheumatic infection in the skeletal system. The main signs and symptoms were related to the pericardium and pleura (left pleural effusion), it is probable that the abdominal symptoms were, to some extent, due to rheumatic peritonitis as well as to pain referred from the inflamed serous surfaces above the diaphragm.

An interesting observation that offers additional evidence to prove the existence of pericardial effusion is the change in the electrical axis of the P waves and Q-R-S complexes which occurred in the first week. The appearance and disappearance of a small left pleural effusion were observed in three x-ray plates taken at intervals of several weeks. The x-ray plates did not aid remarkably in detecting or following the progress of the pericardial effusion. The size of the liver diminished gradually within the first three weeks, so that it was felt only at the costal margin on deep inspiration at about the time when it became impossible to elicit the pericardial friction murmur. The leukocyte count ranged between 23,000 and 10,000 during the first six weeks, a few days before the patient left the hospital it was 8,500. The temperature varied daily, usually between 99 and 102 F, during the first five weeks, then it gradually diminished, and for the next three weeks was between 97 and 99 F. For three days in the tenth week there was a rise again to 101, 100.4 and 99.6 F, then the temperature resumed a relatively normal level. From the hospital the patient went to a convalescent home, where he remained for several months and then returned to light work. He has not had any illness in the past two years.

*Abstract of Clinical History of Rheumatic Fever in the Royal Victoria Hospital from Feb 26 to May 18, 1928*—The patient had been in normal good health until the afternoon of Feb 22, 1928, when he began to feel ill, he noticed that on coughing or deep breathing he had a severe pain in the lower right side of the chest. The next morning the pain in the chest was less noticeable but he had pain in the upper part of the abdomen, headache and vomiting. On the third day he felt more ill than ever, his throat felt sore, and he had pain all over the abdomen. One physician who saw him on this day prescribed rest and a milk diet. On the fourth day, another physician was called because the abdominal pain, vomiting and general sense of illness were worse, and he recommended the patient for admission to the surgical ward with a diagnosis of acute appendicitis. The salient features of the observations made by Dr Webster, the intern in Dr Keenan's service, were as follows: "Cheeks are flushed, patient does not appear to be in any great discomfort, throat is slightly red, breathing 26 per minute, pulse 130 per minute, temperature 102.6° F. Slight impairment of percussion resonance and some harshness of breath sounds over right lung base posteriorly. No pericardial or pleural friction rub. Heart sounds are too rapid to be analyzed. The abdomen is flat, moves freely with respiration, on light palpation the skin is hot, there is no rigidity and little if any tenderness, on deep palpation there appears to be generalized tenderness, especially in both kidney regions, anteriorly and

posteriorly Liver and spleen are not palpable White blood cell count 14,200 Urine, slight trace of albumin, otherwise negative" The patient was observed for four days by the surgeons, at no time did he appear acutely ill Vomiting and abdominal pain were the chief symptoms until the third day, when he complained of pain and stiffness of the knee joints, and on the fourth day this latter symptom became the main source of discomfort X-ray pictures of the chest and the abdomen were essentially negative As the heart rate became slower, Dr Webster noted "both sounds clear at apex" on the fourth day, and "heart examined, no abnormal findings" on the fifth day of the patient's stay in the surgical ward Dr Scriver was asked to see the patient and he found "presystolic, systolic and diastolic murmurs" over the heart, the patient was transferred to the medical service with a diagnosis of acute rheumatic fever on the fifth day after admission to the hospital

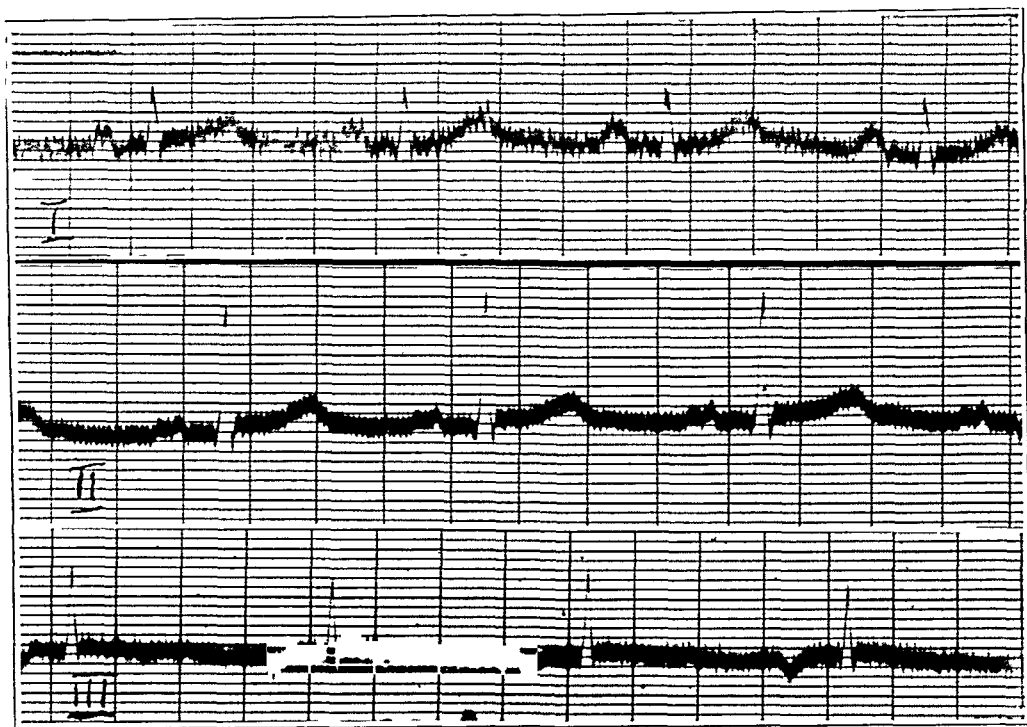


Fig 2—Electrocardiogram recorded on March 6, 1930 Note the shortening of the P-R interval to 0.20 second and the changes in direction and amplitude of all complexes as compared with the previous record Left axis deviation of the P waves suggests enlargement of the left auricle associated with mitral stenosis

The history, taken by the medical intern Dr Jones, revealed that after two days of illness with general malaise, on the evening of February 22, the patient was suddenly seized with a stabbing pain in the chest, beneath the sternum, which lasted all night and prevented him from falling asleep The next morning the pain in the chest was less severe, but he had crampy pains in the abdomen and vomited, the pain in the abdomen was diffuse but worse in the right lower quadrant On the third day, some pain in both knees appeared, but the abdominal symptoms were the chief source of discomfort

The patient recalled vaguely that he first began to have pain over the heart in 1925, and that in 1927 he began to notice shortness of breath on exertion

He remained in the medical ward, in the service of Dr J Kaufmann, from March 2 to May 12, 1928, the illness had all the characteristics of rheumatic fever

with only a moderate degree of swelling of the joints, choreiform movements were noted occasionally, the electrocardiogram showed partial heart block with a P-R interval of 0.26 in the second of three records taken at intervals of several weeks. The heart murmurs were those of mitral stenosis and insufficiency and aortic insufficiency. The record contained frequent notes to the effect that a "friction rub was not heard." One notes, however, that auscultatory cardiac signs were differently described on different days by the same observers as well as by different observers.

#### COMMENT ON CLINICAL OBSERVATIONS

The two periods of illness, separated by an interval of two years, were similar in many respects. Both presented the problem of differential diagnosis between a surgical condition in the abdomen and a pathologic process above the diaphragm, to account for pain in the abdomen. The development of painful swollen joints was the first sign of rheumatic fever in 1928, whereas the almost accidental discovery of a friction rub on the fifth day after the patient's admission to the hospital in 1930 offered some positive evidence to account for the abdominal symptoms. The possibility of rheumatic peritonitis, indeed of rheumatic appendicitis, cannot be entirely ruled out for either of the illnesses. However, the history of pain in the chest at the onset of both illnesses and the observation of the pericardial friction murmur on numerous occasions, mainly with the aid of the shaking method, during the second illness makes it most likely that pericarditis occurred in both. The frequent references to the absence of a pericardial friction rub in the notes of the 1928 illness suggest strongly that this sign was consciously looked for, but apparently no special procedures were adopted in order to elicit it.

The history of this patient's experiences and of the difficulties in diagnosis which he presented to the physicians who saw him lends strong emphasis to the importance of detecting a pleural or a pericardial friction murmur.<sup>10</sup> Fussell and Kay<sup>11</sup> have described 3 cases of rheumatic pericarditis in children whose symptoms were those of acute appendicitis, in each instance the friction murmur was found at the first examination. A fourth case is mentioned in which the friction murmur was discovered immediately after the operation for appendectomy, the surgeon described the appendix as "mildly inflamed."

#### CHARACTERISTICS OF THE PERICARDIAL FRICTION MURMUR AND METHODS OF DETECTING IT

Collin was the first to suggest that the *cui de cum* murmur might be a constant sign of pericarditis in its early stage, the authorities of his

<sup>10</sup> Observations on the pleural friction murmur with the methods described in this communication are being collected and will be described in a future publication.

<sup>11</sup> Fussell, M. H., and Kay, J. A. Symptoms of Appendicitis in Acute Pericarditis, *Am J M Sc* **163** 40, 1922.

generation, Corvisart, Laennec and others, taught that pericarditis could not be diagnosed clinically. However, beginning with the work of William Stokes (1834), a long line<sup>12</sup> of keen students of clinical medicine have made numerous valuable contributions to the development of methods of investigation and of diagnostic thinking for the detection of pericarditis. A composite description of these contributions may be made in a few sentences and is to be found in the modern textbooks on heart disease. The *en de cun* murmur is indeed typical of the pericardial friction sound, but it is not a *sine qua non* to the diagnosis of fibrinous pericarditis. Short, soft to-and-fro murmurs, swishing to-and-fro or single murmurs and coarse or rasping murmurs, any of which may resemble some intracardiac or so-called functional murmur or may seem to be "close to the ear" and thus suggest pericarditis, have been heard and described in cases of acute fibrinous or serofibrinous pericarditis. Although the friction murmur is usually heard over a small area of the sternum, it may be restricted to any small area of the precordium or may be audible all over the area of relative cardiac dulness. It is extremely rare to hear it beyond the cardiac area, or over the back. By increasing the pressure with which the stethoscope is applied to the chest, the loudness of the murmur may be increased, by changing the posture of the patient, the loudness may also be varied. The pericardial friction murmur in any given case is apt to be unstable, it may appear and disappear like a jack-in-the-box, its loudness and quality may change remarkably, either gradually or with great suddenness. This instability is a valuable diagnostic feature.

Those who have written about the pericardial friction murmur have invariably adopted the point of view that is manifested in the foregoing paragraph. The discovery of a murmur is assumed, and ways and means of differentiating it are described. The general principle of these methods of distinguishing the murmur is similar to that of the methods used in differentiating various endocardial murmurs. Experience in recent years has made it clear that any general discussion of the pericardial friction murmur (and also of the pleural friction sound) should begin with, or should at least include, the description of methods for eliciting the murmur when it is not heard during the usual routine procedures of auscultation. As the mental attitude of clinicians to the

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12 Hope, James. A Treatise on the Diseases of the Heart and Great Vessels, London, W. Kidd, 1832. Bouillaud, J. B. *Traité clinique des maladies du cœur*, Brussels, H. Dumont, 1836. Skoda, J. *Abhandlung über Perkussion und Auscultation*, Vienna, L. W. Seidel, 1839. Latham, P. M. *Diseases of the Heart*, Philadelphia, E. Barrington & G. D. Haswell, 1847. Gibson, Francis. *Pericarditis*, in Reynold, J. R. *A System of Medicine*, Philadelphia, J. B. Lippincott Company, 1877, vol. 4. Sansom, A. E. *Manual of the Physical Diagnosis of Diseases of the Heart*, Philadelphia, P. Blakiston, 1881.

pericardial friction murmur will change from that of expecting it to arrest their attention to that of consciously searching for it with the aid of all known methods, fewer cases of acute pericarditis will escape them. The accumulated clinical and pathologic experience of various observers during the past century makes it possible to list the types of cases in which the existence of serofibinous pericarditis should be suspected. A recent analysis by Gerke<sup>13</sup> of the etiology of pericarditis based on the records of 26,771 postmortem examinations and 75,856 clinical case histories, offers valuable statistical data. These records represent observations made in three general hospitals and in one hospital for infectious diseases of Moscow (Russia) during the past twenty years. Pericarditis occurred most frequently in rheumatic infections; it was found at autopsy in 245 instances, and the clinical diagnosis was made in 91 cases which were not examined post mortem, these 336 cases represent 19.1 per cent of all the rheumatic cases. For tuberculous and pneumococcic infections, the incidence of pericarditis is 15.6 and 14.2 per cent, respectively, for nephritis it is 9 per cent, for infectious diseases (scarlet fever, measles, smallpox and diphtheria), 14.7 per cent and for a variety of conditions—influenza, pyemia, myocardial infarction—20.6 per cent, there were 53 cases (2.5 per cent) in which no etiologic factor could be determined. White<sup>2b</sup> quoted a series of 244 cases of acute pericardial disease observed post mortem and reported by Preble (1901), pneumonia was the etiologic factor in 34 per cent, rheumatic fever in 28.4 per cent, nephritis (uremia) in 11 per cent, tuberculosis in 10 per cent, sepsis in 4.7 per cent, cardiac infarction and aneurysm of the heart or aorta in 2.6 per cent and typhoid fever in 1.7 per cent. He also referred to Stone's series (1919) of 300 cases of death from pneumonia in an army base hospital, 24 per cent of these showed acute pericarditis at autopsy. The presence of an etiologic factor for pericarditis is of more significance in arousing one's interest in discovering a friction murmur than the presence or absence of symptoms such as pain in the chest, cyanosis, dyspnea, tachypnea and abdominal symptoms, for pericarditis frequently exists without causing any such symptoms.

On analyzing the possible reasons for the instability of the pericardial friction murmur, there appear suggestions for clinical methods of eliciting it. The murmur is produced by the rubbing movement of the two pericardial surfaces lining the pericardial cavity, when fibinous exudate is present on one or both of them. On the other hand, the murmur vanishes when these two layers are separated by fluid exudate or when the fibinous exudate becomes sufficiently organized to cause fixed adhesion of the two layers of pericardium or when the organization

<sup>13</sup> Gerke, A. A. Die Ätiologie der Pericarditis, Virchows Arch f. path. Anat. **278** 1, 1930.

and healing result in the smooth so-called milk patch. The separation of the two layers of pericardium by exudate may be only temporary, depending on the variations in the amount of fluid, as determined by the balance between exudation and resorption and by the disposition of the fluid in the pericardial sac. Thus, the murmur may appear, disappear and reappear. During these transitions, the quality, loudness and position of the murmur may vary. Following an attack of acute serofibrinous pericarditis there may remain a more or less close network of fibrous pericardial synechiae, enclosing spaces of normal pericardial surfaces, in a second attack of acute pericarditis the inflammatory lesions may be patchy in their distribution, and there may be different stages of the evolution of the pericarditis in the various spaces at different times. Such conditions would result in the permanent disappearance of a friction murmur over one area of pericardium and its appearance over another. Moreover, in the small restricted spaces, variations in the amount and disposition of serum are apt to have a great effect on the character and the presence or absence of the murmur.

Curschmann<sup>14</sup> and, more recently, Conner<sup>15</sup> have drawn attention to anatomic features of the position of the heart within the chest which make it clear that even when large amounts of fluid are present in the pericardial sac, only a thin layer can exist between the two layers of pericardium on the anterior surface, because the heart lies quite snugly interposed between the sternum and the spinal column, pericardial effusions accumulate laterally. Conner, therefore, emphasized the fact that the accumulation of a large amount of pericardial effusion does not necessarily imply the disappearance of the friction murmur, and he described observations which prove this to be true. Thus, whether the pericardial effusion accompanying the fibrinous exudate is large or small and whether the area of pericarditis is small or widespread, the pericardial friction murmur may be observed to appear and disappear as long as there is fibrinous exudate on one or both surfaces, at or near the anterior aspect of the heart. Under such conditions, any procedures that will cause the separated inflamed surfaces to be brought into contact with one another will be effective in eliciting the murmur.

It is well known that under normal conditions the position of the heart in the chest cavity changes appreciably during deep respiration and with variations in posture. The heart may be said to be suspended from the inferior and superior venae cavae and the arteries which leave the arch of the aorta to go to the head. Consequently, with changes in posture or variations in the height of the diaphragm, the heart swings or

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14 Curschmann, H. *Deutsche Klin* **15** 401, 1907

15 Conner, L. A. On the Diagnosis of Pericardial Effusion, *Am Heart J* **1** 421, 1926

rotates around this axis. Under normal conditions, the negative pressure in the chest causes a fixed relation between the two layers of pericardium so that the parietal layer moves *pari passu* with the heart, as the position of the heart alters during changes in posture of the body or during movements of the diaphragm. When there is a pericardial effusion, the difference in the specific gravity of the fluid and of the heart makes it possible for the heart to move over a greater arc than the parietal pericardium, the heart, being heavier, will displace fluid in an upward direction. Because the heart fits in so closely between the sternum and the spinal column, little movement in the antero-posterior direction can occur. On the other hand, both because the bulk of fluid accumulates on the lateral aspects of the heart and because the lungs are compressible, the heart moves much more freely from side to side. It is mainly the movement of the heart within the pericardial cavity that causes changes in the disposition of the fluid exudate and brings about the instability of the pericardial friction murmur. Thus, the same procedures that may help to elicit the murmur may cause it to disappear. This phenomenon lends itself very well for use as a test to differentiate the friction from other cardiac murmurs.

The procedure of shaking the chest, which proved so successful in the case described, is but one of the many methods of altering the position of the heart. It seems, however, to have certain advantages which under suitable circumstances make it the method of choice. The simpler methods may be tried. 1. Deep breathing, coughing, sighing, yawning and sneezing, chiefly in virtue of the movements of the diaphragm, cause changes in the lie of the heart which may affect the presence or absence of a pericardial friction murmur. 2. A second group of procedures consists of changes in the posture of the patient, performed slowly or rapidly, the greatest amount of movement of the heart will take place during a shift from one lateral recumbent position to the other. Closely related to the shaking procedure is voluntary movement of the patient from side to side as he occupies the knee-chest position, or from the dorsal to the prone position as he lies on one side. This last procedure is a relatively gentle and effective one, it is suitable for the observation of rather heavy persons and is applicable to sick patients in whom it can be carried out at a slow rate, the patient being entirely passive. Another postural change that merits being mentioned is that from the recumbent to the sitting posture, Corrigan observed the appearance and disappearance of the pericardial friction murmur with this procedure in 1842. The various respiratory and postural movements may be combined, thus, deep respiration in the knee-chest position is likely to elicit the murmur, to alter its character and location or to cause it to vanish.

When the murmur is of the typical to-and-fro, leathery, creaking type it leaves no doubt as to the existence of pericarditis. But it may resemble any of the endocardial or exocardial murmurs, which also vary with respiratory and postural changes, so that other differentiating characters become necessary. Perhaps the most important of these is the transitory nature of the pericardial murmur, which is elicited by any of the foregoing procedures. It is likely to be heard for only a few moments or minutes, and repeated maneuvers may be required to elicit it again. The same procedure that caused the murmur to appear may cause it to vanish. It may be heard after one procedure at a given time, and only after another procedure at another time. On the other hand, the murmurs from which it must be differentiated have a constant relation to the postures in which they are present or absent, if one of these murmurs is audible only in the recumbent posture, it persists as long as the patient maintains this posture, and this may be readily observed at any time in the course of days or months. The friction murmur that is elicited repeatedly by the same or different procedures may vary in quality, in loudness and in position each time it is heard, whereas for the other murmurs these characters are quite constant.

On a priori grounds, conditions that would prevent variations in the friction murmur must be recognized. Thus, given a certain degree of organization with fibrous adhesion in the midst of an area of fibrinous exudate, the two layers of pericardium would be sufficiently fixed at this point to make it impossible to separate them enough to cause the murmur to vanish, or perhaps even to alter its loudness or quality. Under such circumstances, the friction murmur is to be heard with equal loudness and at the same point in all postures and after shaking. It disappears only when the process of fibrosis and fixed adhesion is completed. One would, however, most likely find that the friction murmur over other portions of the precordium would vary with different procedures which alter it when there are no fibrous synechiae.

Whereas the respiratory and postural movements seem simpler procedures than that of shaking or rolling the patient's body, the latter have a number of advantages which make them the methods of choice. (1) By shaking or rolling the heart is moved rather quickly in many directions, (2) it is much less fatiguing for the patient to be moved passively than to perform a series of voluntary movements, (3) in differentiating the friction murmur from other murmurs, the elements of change in posture and respiratory phase which affect these murmurs are eliminated, for auscultation is carried out under the same conditions before and after shaking or rolling. It has repeatedly been observed that after the pericardial friction murmur has been elicited by a given change in posture, it may be caused to vanish or reappear or to change in loudness, quality and position by the shaking method. In cases of



repeated pericarditis the acute inflammation is limited to spaces bounded by the fibrous adhesions resulting from previous attacks, the heart does not move sufficiently with changes in posture or during respiratory variations to affect the conditions that determine the presence or absence of a pericardial friction murmur. The case reported is an example of this type of condition, in which the shaking method is the most effective in eliciting the murmur.

#### CONCLUSIONS

The pericardial friction murmur is a clinical sign the detection of which depends on methods of eliciting it and of differentiating it from other murmurs that may be heard over the precordium. From the point of view of the observer in search of clinical signs the discovery of a typical leathery friction rub in the course of an ordinary examination of the heart may be looked on as a fortunate accident.

Respiratory movements, postural changes and shaking or rolling of the body may cause a pericardial friction murmur to appear, to vanish and to reappear, and they may alter the loudness, quality and position of the murmur. These procedures, therefore, constitute methods of eliciting a friction murmur and of differentiating it from other murmurs which it may resemble.

# ACUTE LEUKEMIA FOLLOWING LYMPHOSARCOMA

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AND  
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Lymphosarcoma and lymphatic leukemia have been regarded as two distinct pathologic conditions. In recent years, however, the leukemic state has come to be regarded as merely a phase of circulating metastases from lymphosarcoma. This implies that all patients with leukemia present the condition of lymphosarcoma earlier in their histories, and that this condition may not have been clinically evident because of the deep location of the involved lymph nodes.

A review of the entire literature for the presentation of evidence proving the correctness of the hypothesis stated is beyond the scope of this report. However, attention may be called to the more recent reports which deal with cases similar to the ones we present.

Evans and Leucutia,<sup>1</sup> in 1926, treated sixteen patients who had lymphosarcoma with deep roentgen therapy, all showed a uniformly rapid subsidence of symptoms. The exact dosage employed in these cases is not stated by the authors, but usually after from five to ten therapeutic exposures, the sarcomatous swellings disappeared and the general condition of the patients so improved that they were permitted to resume their respective occupations. This same degree of radiosensitivity was also seen in the leukemic cells in the circulating blood, for their number promptly dropped if the therapy was applied at the time of a high lymphocyte count.

Among the sixteen patients so treated, however, there were three young adults who in from one to three months after their discharge returned to the hospital with the typical clinical picture of acute lymphatic leukemia, which progressed rapidly to a fatal termination. Similar cases with an identical clinical and therapeutic course were first described by Wagner<sup>2</sup> and by Webster<sup>3</sup> in 1920. Other cases of

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From the Departments of Pediatrics and of Surgery, the University of Chicago.

1 Evans, W. A., and Leucutia, T. The Neoplastic Nature of Lymphatic Leukemia and Its Relation to Lymphosarcoma, *Am J Roentgenol* **15** 497 (June) 1926.

2 Wagner, R. Leucosarcomatose (Sternberg), *Wien med Wchnschr* **70** 1655, 1920.

3 Webster, L. T. Lymphosarcoma, Lymphatic Leukemia, Leucosarcoma, Hodgkin's Disease, *Bull Johns Hopkins Hosp* **31** 458, 1920, *Johns Hopkins Hosp Rep* **20** 251, 1921.

TABLE 1—Cases of Leukemia Following Lymphosarcoma

Author, Year	Sex, Age	Origin	Blood Picture at Outset	Therapy	Effect of Therapy	Development of Leukemia	Autopsy Final Diagnosis
Wagner, 1920	Male, 5 years	General lymphadenopathy with mediastinal tumor	Normal, but large lymphocytes predominated	3 daily exposures, 5 later	Disappearance of lymphadenopathy	6 weeks, white cells, 300,000 (small lymphocytes)	Leukosarcoma
Webster, 1921	Male, 28 years	Localized tumor of the chest	Normal, white cells 3,900	Half an hour daily for 10 days	Leukemia white cells, 31,000, with echthymoses	Immediately after treatment	No record
Evans and Leucutia, 1926	(1) Male, 23 years (2) male, 15 years (3) Male, 21 years	Mediastinal gland Mediastinal gland Generalized lymphadenopathy	Normal white cells, 14,100 (polymorpho nucleurs 72%) Normal white cells 12,500 (polymorpho nucleurs 64%) Normal white cells 8,600 (polymorpho nucleurs 78%)	Irradiation for 10 days Irradiation for 10 days Irradiation	Disappearance of tumor white cells, 2,200 Rapid improvement white cells, 200 Improvement white cells, 600	1 month, metastatic nodules on scalp white cells, 144,000 5 months, pain in legs, mass in left testicle, white cells, 300,000 5 months, numerous nodules of the skin, white cells, 81,000	Lymphosarcoma, with marked changes in marrow None Lymphosarcoma of lymph gland and bone marrow
Borchardt, 1927	Male, 43 years	Mediastinal gland	Normal	Irradiation	Improvement white cells, 6,800	7 months, white cells, 100,800 (lymphocytes 98%)	Lymphatic leukemia
Kneal, 1927	Male, 7 years	Mediastinal mass	White cells, 12,600 (polymorpho nucleurs 82%)	Several roentgen ray exposures	Decrease of mass in 1 month	1 month, hemorrhage and pallor, white cells, 531,000 (lymphocytes 80%)	No record
Young and Spalding, 1928	Male 8 years	Mediastinal gland	White cells, 22,000 (polymorpho nucleurs 76%)	Irradiation	White cells, 1,016,000 (lymphocytes 93%)	2 weeks	Mediastinal lymphosarcoma
Hensel, 1928	Male, 13 years	Mediastinal tumor	White cells 13,000 (polymorpho nucleurs 78%)	Irradiation	White cells, 832,000 (lymphocytes 97%)	Several months	Lymphosarcoma (thymus)
Flashman and Leopold, 1929	Male, 60 years	Inguinal gland	Slight lymphemia, white cells, 7,300	3 weekly for 4 months	Improvement white cells, 5,000 and 7,000	4 months white cells, 96,000 (lymphocytes 90%) 1 month, white cells, 76,000 (lymphocytes 87%)	Lymphosarcoma, leukemia metastases
Landau, 1930	Male, 5 years	Generalized lymphadenopathy, mediastinal tumor and left pleural exudate	Normal white cells, 13,200	Röntgen rays	Marked improvement, white cells, 5,100		
Cooke, 1932	(1) Male, 12 years (2) Male, 5 years	Mediastinal tumor Mediastinal glands	Normal, white cells, 9,200 (polymorpho nucleurs 71%) Normal, white cells, 12,200 (polymorpho nucleurs 61%)	5 daily exposures 5 daily irradiations	Marked improvement, white cells, 6,200 Disappearance of enlargement	6 weeks white cells, 110,000 (lymphocytes 98%) 5 weeks, recurrence of enlargement and echthymoses white cells, 33,000 (lymphocytes 92%)	None None
	(3) Male 5 years	Mediastinal gland	Normal	2 days irradiation	Disappearance of skin, but mass persisted white cells, 8,400	2 months white cells, 77,200 (lymphocytes 92%)	None
	(4) Male, 35 years	Mediastinal gland	Normal	4 days white cells, 21,400 (polymorpho nucleurs 76%), no abnormal cells	Disappearance of mass, white cells 2,100 (polymorpho nucleurs 75%)	2 months white cells, 317,000	None

lymphosarcoma terminating in leukemia after deep roentgen treatments have been reported by Borchardt,<sup>4</sup> Kneal,<sup>5</sup> Young and Spalding,<sup>6</sup> Hensel,<sup>7</sup> Flashman and Leopold<sup>8</sup> and Landau.<sup>9</sup> Recently Cooke<sup>10</sup> collected from the literature seventy-four cases of mediastinal tumors associated with leukemia and reported several similar cases of his own. Four of the patients came under his observation in the "preleukemic" stage, but after the institution of roentgen irradiation, terminal leukemia developed in all. The summary of the cases previously reported is given in table 1.

In the light of the preceding brief review of the literature, the two cases herein presented are of special interest, in that the same combination of symptoms and course is illustrated.



Fig 1—Photograph of patient, M. K., taken on first admission to hospital in January, 1932, showing the swelling of the left parotid and cervical regions.

#### REPORT OF CASES

CASE 1—*History*—M. K., a 5 year old girl, came to the University of Chicago Clinics on Jan 7, 1932, with the complaint of swelling of the left side of the face (fig 1). The swelling began to appear insidiously six months prior to presenta-

4 Borchardt, H. Beitrag zur Frage der Gewachse mit leukamischen Blutbild, Verhandl. d. deutsch. path. Gesellsch. **22** 96, 1927.

5 Kneal, E. A Case of Lymphatic Leukemia, Am. J. Dis. Child. **33** 541 (March) 1927.

6 Young, G. J., and Spalding, J. E. Report on a Case of Lymphosarcoma of Thymic Origin with Acute Lymphoid Leukemia, J. M. Soc. New Jersey **25** 609, 1928.

7 Hensel, O. A Case of Leukosarcomatosis, M. J. & Rec. **128** 528, 1928.

8 Flashman, D. H., and Leopold, S. S. Leukosarcoma, with Report of a Case Beginning with a Primary Retroperitoneal Lymphosarcoma and Terminating with Leukemia, Am. J. M. Sc. **177** 651, 1929.

9 Landau, A. Ein Fall von Lymphosarkom mit terminalem leukamischen Blutbild, Ztschr. f. Kinderh. **48** 614, 1930.

10 Cooke, J. V. Mediastinal Tumor in Acute Leukemia, Am. J. Dis. Child. **44** 1153 (Dec.) 1932.

tion There was no sore throat, corvza, earache, cough or fever at any time preceding or during the development of the swelling Tonsillectomy had been performed three months previously, but no change in the size of the swelling was noticed The swelling was not painful but it was tender to pressure The patient had been up and about and not confined to bed at any time The swelling was apparently quite different in nature from a similar swelling on the opposite side which had developed two years previously, and which was satisfactorily treated by incision and drainage Otherwise, the patient's past history was irrelevant, and there was nothing of consequence in the family history

*Examination*—Physical examination revealed a well developed but poorly nourished white girl, not acutely ill The positive findings were (1) a large swelling

TABLE 2—*Blood Picture in Case 1*

Date	Red Cells, Mil lions	Hemoglobin (Sahli and Newcomer) per Cent	White Cells	Platelets	Differential					Reticu- loocytes, per Cent
					Lym- pho cytes	Poly morpho nuclears	Mono nu- clears	Posino phils	Baso phils	
1/ 8/32	5.30	98	6,200		26	72	2	0	0	
1/17/32	5.70	11.2	4,500	300,000	16	79	4	1	0	0.9
2/22/32	2.74	5.1	179,200	38,000	98	2	0	0	0	
2/23/32					93	7	2	1	1	
2/29/32	0.90	4.5	18,000	20,000	94	4	0	1	1	

TABLE 3—*Roentgen Treatment in Case 1\**

Date	Area Exposed, Diameter	Area Treated	Dosage (Air Value), Roentgens
1/11/32	15 cm	Left cervical and submaxillary glands	412.5
1/12/32		Left cervical and submaxillary glands	137.5
1/13/32	10 cm	Anterior left axilla	206.0
	10 cm	Anterior right axilla	206.0
1/14/32	10 cm	Anterior left axilla	206.0
	10 cm	Anterior right axilla	206.0
1/15/32	20 cm	Both inguinal glands anteriorly	206.0
1/16/32	15 cm	Anterior thorax (for mediastinum)	275.0
1/18/32	10 cm	Left cervical and submaxillary glands	206.0

\* The patient was treated at the University of Chicago Clinics. The tube was impressed with 150 kilovolts peak (sphere gap). The filter used was 0.25 mm. of copper plus 1 mm. of aluminum, the effective wave length, 0.187 angstroms, and the focus skin distance, 50 cm.

over the parotid area on the left side of the face, involving the upper third of the neck, it was firm, hard, most prominent at the angle of the jaw and not tender or fluctuating, (2) a firm mass measuring 2 by 1.5 cm. in the submental region, (3) a slight enlargement of the postauricular glands, (4) swollen ampulla of the left Stenson's duct, (5) a hyperemic pharynx, and (6) moderate malnutrition. Roentgen examination of the region of the neck and of the chest did not show a pathologic condition of the bones or lungs, and the blood picture was entirely normal, as is shown in table 2.

Two days after admission, biopsy of the large tumor of the left parotid region revealed a heavy invasion of uniform-appearing lymphoblasts obviously not far removed from the normal lymphocytes. The pathologic diagnosis was lymphoblastoma (of the Paltauf type) which had broken through the capsule and infiltrated the surrounding tissues (fig. 2). Under an oil immersion lens, the lymphoblasts showed evidence of active proliferation, as each field contained from two to five mitotic figures (fig. 3).

*Treatment and Course*—The therapeutic measures adopted were saturation therapy at two day intervals of the lymph nodes of the left cervical region and generalized irradiation of other lymphatic areas. The irradiation was carried on under the supervision of Dr Charles S Capp of the department of roentgenology, and the technical details are given in table 3.

The blood count made at the conclusion of the treatment showed again a normal picture, with, however, decided leukopenia and a normal differential count.

As a result of the roentgen therapy, the tumor mass on the left side of the face disappeared almost completely, and the patient was discharged.

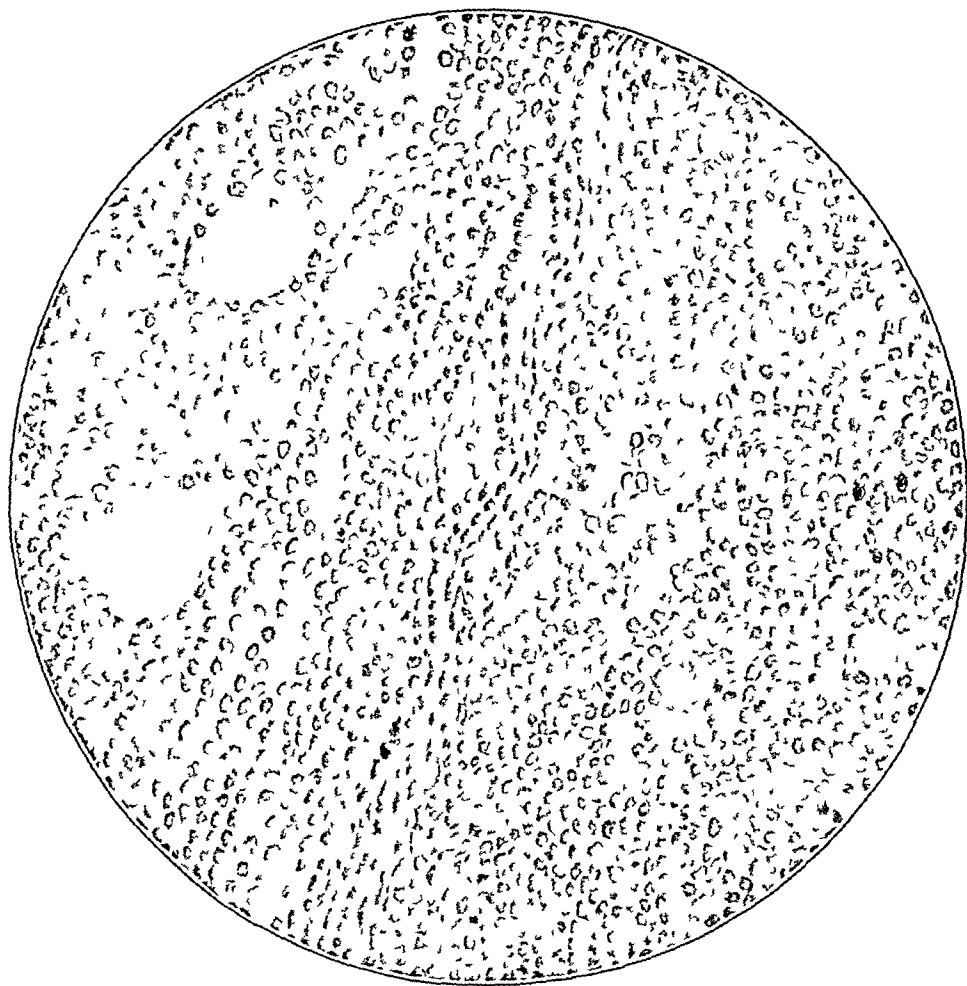


Fig 2—Histologic specimen of the cervical lymph gland removed at biopsy, Jan 9, 1932. The parenchyma of the gland is a mass of proliferating lymphoblasts which have invaded the extracapsular areolar tissue, with thinning of the capsule. The section was embedded in paraffin and stained with hematoxylin and eosin. The drawing was made with camera lucida, a 4 mm objective and 5 $\times$  ocular being used.

The patient remained well for about four weeks, at this time her parents again noticed the swelling at the same place. It grew for two days. They further noticed that the child would easily acquire black and blue marks and that there was bleeding from the nose and mouth. The appetite began to fail, and a slight rise in temperature was also noted. The mother found one day that the child's urine was blood-tinged. The patient was readmitted to the hospital, and physical

examination revealed (1) signs of hemorrhages from nose and mouth, (2) purpuric spots in various parts of the body, (3) enlarged cervical glands, (4) palpable spleen, (5) hematuria and (6) prolonged bleeding time

Examination of the blood disclosed the true nature of the disease, as is seen in table 2. The tissue culture of the blood cells was made by Dr. William Bloom of the department of anatomy, who stated that the predominating cells did not show active tendencies to differentiate into myeloid types, a fact which supported the assumption that they were lymphocytic.

After a transfusion of blood had been made, the patient was discharged, against advice. One week later, the child was brought to the hospital for the third time.

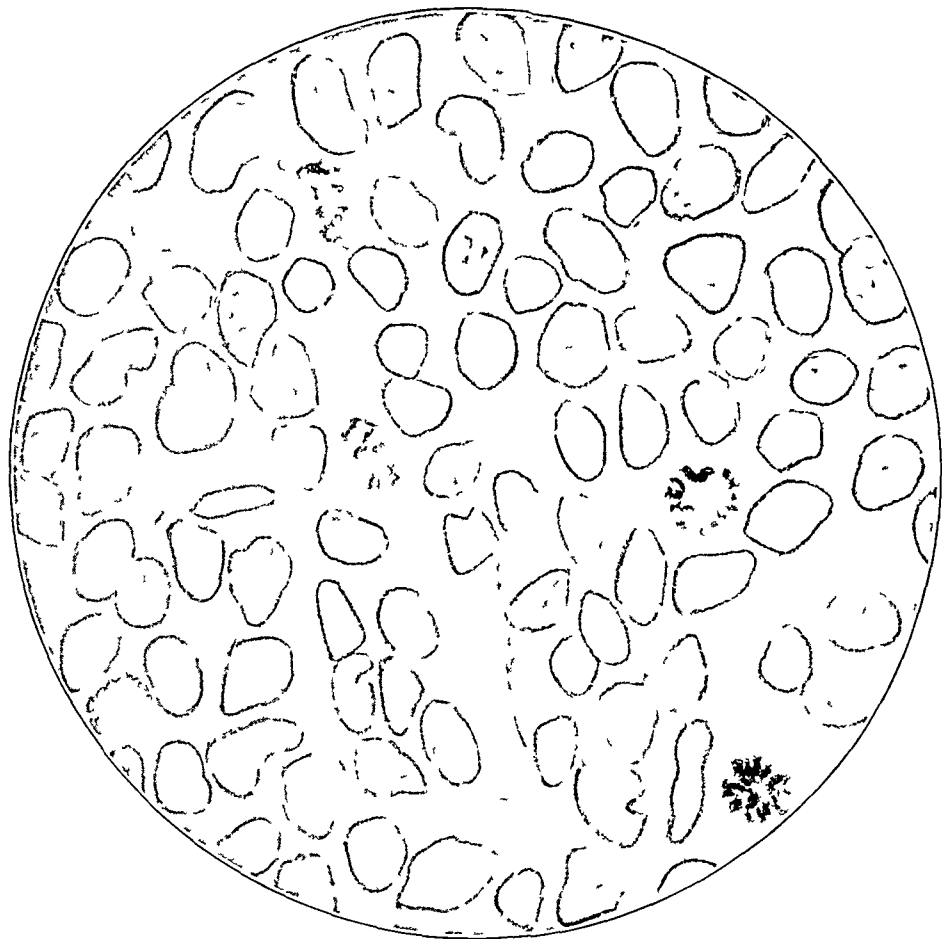


Fig. 3—A portion of the parenchyma of the lymph gland shown in figure 2, seen under an oil immersion lens, 1.9 mm., with 10 × ocular, showing five mitotic figures in the field.

She had been failing steadily and was found to be moribund. Ecchymotic areas were multiplied over the entire body. The spleen and the liver were large. Examination of the blood showed a general reduction in the number of both the red and the white cells. Another transfusion was given, but the patient continued to be lethargic. She died on the third day after admission.

*Autopsy*—At autopsy, which was performed by Dr. Eleanor M. Humphreys of the department of pathology, the most striking picture was that of the numerous petechial hemorrhages found over the surfaces of the heart and the lungs (fig. 4).



Fig 4—The heart and the lungs of the patient in case 1, removed at autopsy on March 2, 1932, by Dr E M Humphreys, showing numerous petechial hemorrhages over the surfaces of the organs

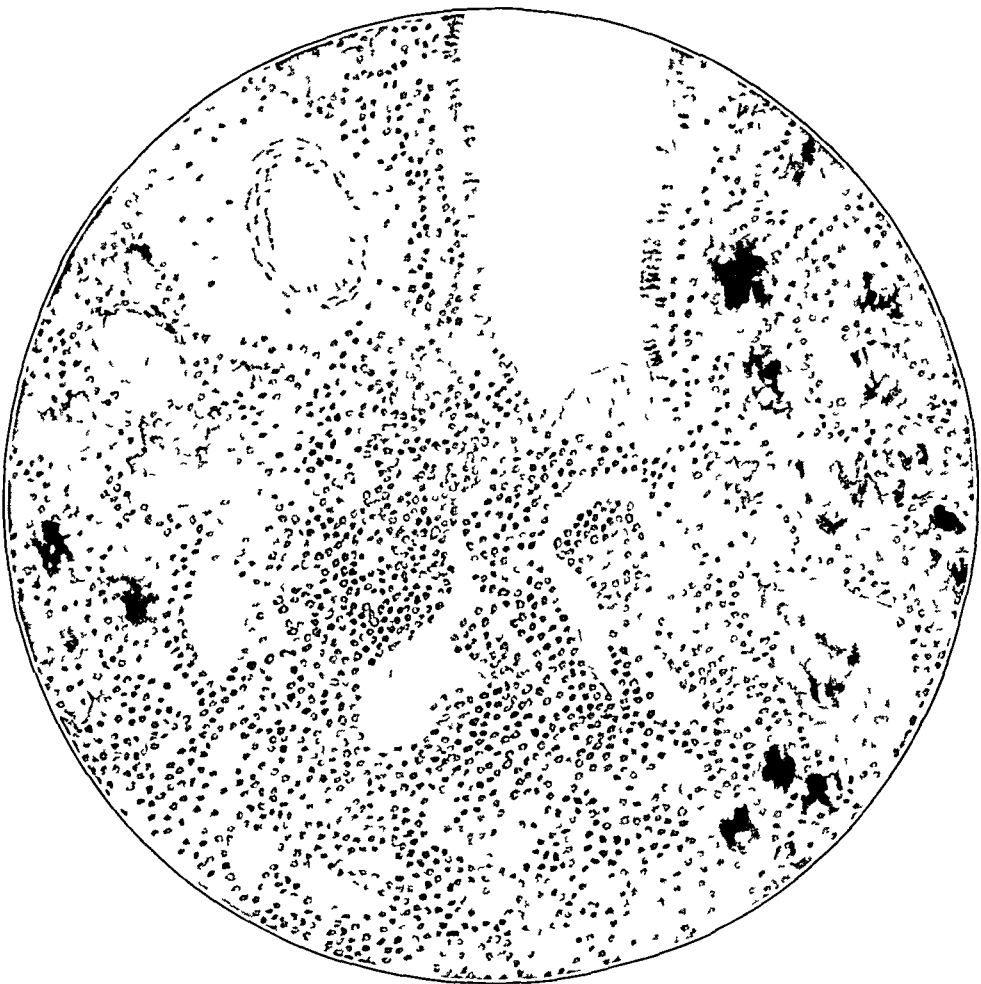


Fig 5—A section of the lung in case 1, showing a moderate amount of lymphocytic infiltration around a bronchiole, together with hemorrhagic infarcts and coagulation necrosis. The section was embedded in celloidin and stained with hematoxylin and eosin. Camera lucida drawing, with a 4 mm objective and 5 × ocular



The purpuric spots were also found on the skin in general, but were particularly marked over the extremities. There were also extensive submucosal hemorrhages in the pelves and the calyces of both kidneys, which extended down to, and stopped sharply at, the ureteropelvic junctures. Microscopically, contrary to our expectations, the sections of various organs showed a rather scanty evidence of lymphocytic infiltration. The only evidence consisted of the slight infiltration around some of the bronchioles in the lungs (fig 5) and a slight hyperplasia of the lymphoid elements in the intestinal mucosa (fig 6). The spleen showed only moderate hyperplasia and the liver extensive central necrosis involving practically all

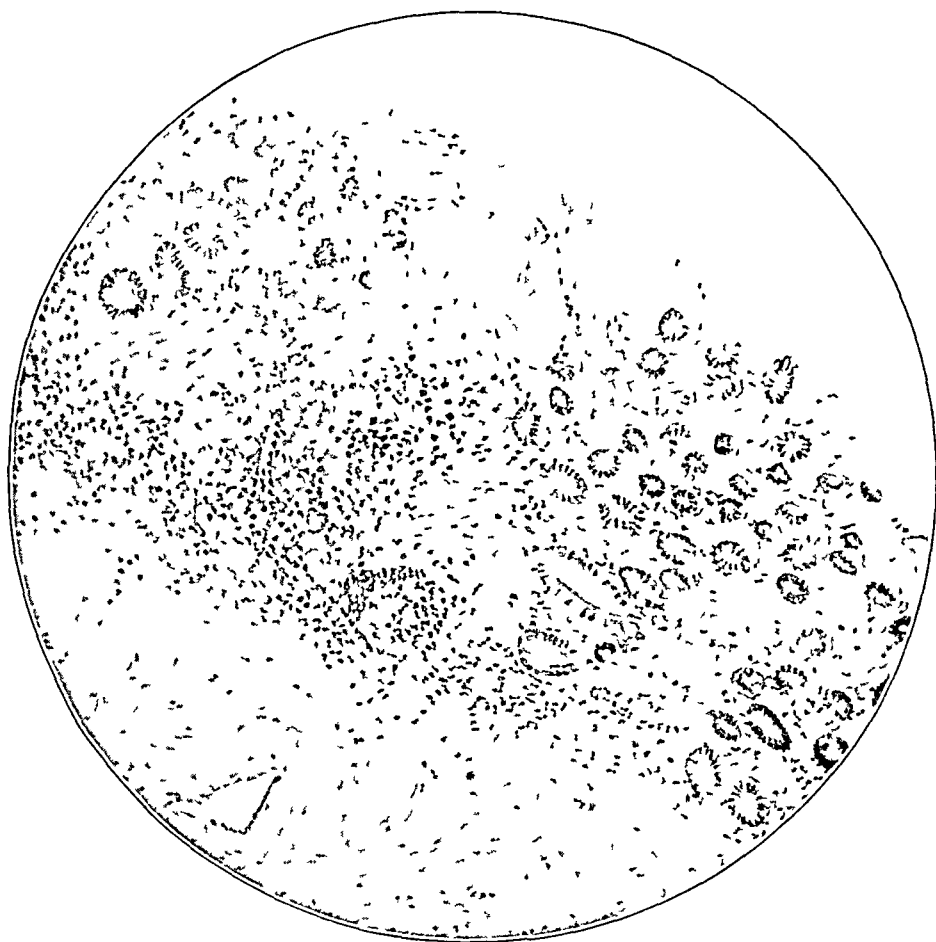


Fig 6—A section of the large intestine, showing a slightly abnormal lymphocytic infiltration of the mucosa, with a small necrosis on the surface. A celloidin section, stained with hematoxylin and eosin. Camera lucida drawing, with a 4 mm objective and 5 × ocular.

of the lobules, without, however, any inflammatory reaction. In the kidneys was found a scattered area in the interstitial tissue which contained pyknotic and fragmenting nuclei, again without any inflammatory changes. The bone marrow was edematous and rather scanty in the myeloblasts and erythroblasts. The presence of mycotic emboli in the lungs and in some lymph nodes was also noted. Many healing encapsulated tubercles were also found in various organs.

CASE 2—*History*—A S., a 9 year old boy of Polish parentage, entered the Children's Memorial Hospital on Aug 31, 1931, with a complaint of difficulty in

breathing and spells of choking. His mother stated that about one month previously he had complained of headache, abdominal pain and, especially, a feeling of pressure under the sternum. He coughed frequently, slept restlessly and ate poorly. He had lost 8 pounds (3,600 Gm) during the month prior to admission.

The past history indicated that he had never been robust. He was a full term baby. The labor was difficult, and terminated with a version and extraction. The right humerus was fractured at delivery, and an injury to the cervical nerves occurred, producing an Erb's palsy. When the patient was 13 months of age, he was operated on in an attempt to repair the injury done to the arm at birth. This operation was only partially successful, as he suffered trophic disturbances in the skin of the hand and arm at various times.

*Examination*—Physical examination revealed a poorly nourished and developed boy who breathed with considerable difficulty (fig 7). The tonsils were slightly injected but not markedly enlarged. The anterior and posterior cervical lymph



Fig 7—Photographs of the patient, A S, taken at various stages of the disease. 7 A, taken on Sept 1, 1931, shows the tumor mass over the upper part of the anterior portion of the wall of the chest, 7 B, taken on September 29, shows bilateral cervical enlargement. About this time the hospital record shows a rise in temperature to 104 F, which persisted until death on October 14. In 7 C, taken also on September 29, numerous purpuric spots over the lower extremities are shown.

nodes were pea-sized. The trachea and larynx were displaced to the right of the midline by a mass which bulged out into the left supraclavicular region, and which was continuous with a nodular swelling projecting 1.5 cm above the wall of the chest and measuring 4 cm in diameter in the left infraclavicular region. The superficial veins of the chest and abdomen were distended. The respiratory excursions of the left thoracic wall were definitely limited, and the percussion note was dull over the left side of the chest anteriorly and posteriorly. Over the upper part of the lungs, the breath sounds were tubular, and below the angle of the scapula they were suppressed. The right lung was hyperresonant and the breath sounds exaggerated. The heart was displaced to the right, the point of maximum impulse being in the fifth interspace just to the right of the sternum. The tones were

muffled and distant, but no murmur was heard. The liver was palpable two finger-breadths below the costal margin, no other masses were palpable in the abdomen. The left arm and the legs were normal. The inguinal, axillary and epitrochlear lymph nodes were not enlarged.

The urine showed a trace of albumin. The blood counts made at various stages of the disease are summarized in table 5.

The roentgenograms (fig 8 *A*) showed a wide, dense mediastinal shadow measuring 11 cm in width and extending from the second thoracic vertebra to the diaphragm. This shadow could not be separated from the shadow of the heart, and was thought to be due to a mass of tumor glands. A slight clouding of the upper two lobes of the left lung and dense clouding of the lower lobe were thought to be caused by a partial atelectasis due to compression by the tumor mass.

*Diagnosis*—At this time a diagnosis of mediastinal tumor was made and deep roentgen therapy was instituted at Grant Hospital, as shown in table 4. After the third treatment, the appearance of the patient was quite different from that noted

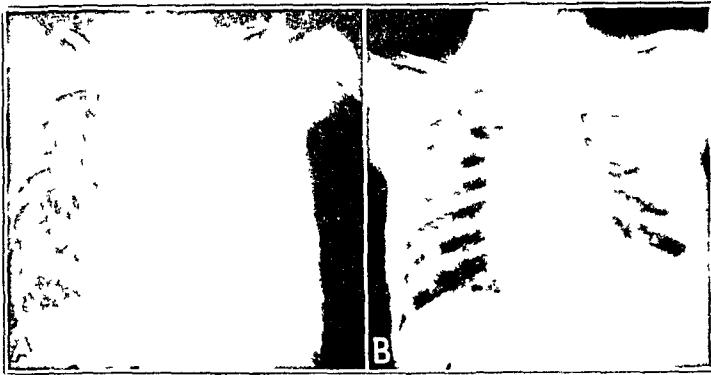


Fig 8—Roentgenograms of the chest in case 2, *A*, taken on Aug 29, 1931, shows the mediastinal tumor mass with left pleural exudate, and *B* (taken on September 9, after a course of deep roentgen treatments) shows the disappearance of the tumor and of the exudate.

TABLE 4—*Roentgen Treatment in Case 2\**

Date	Kilo Voltage	Area Treated	Dosage in Milliamperes Minutes
9/3/31	130	Anterior left part of the chest and mediastinum	175
9/4/31	130	Anterior left part of chest and mediastinum	100
9/5/31	140	Posterior left part of chest and mediastinum	100
9/8/31	140	Posterior left part of chest and mediastinum	125
9/9/31	140	Posterior left part of chest and mediastinum	50
	140	Anterior left part of chest and mediastinum	75

Patient was instructed to return in one month for further treatment.

\* The patient was treated at the Grant Hospital, Chicago. The voltage of the tube was determined by a calibrated spherical gap. A filter of 0.25 mm of copper plus 1 mm of aluminum was employed. The focal skin distance was 50 cm, the area of exposure, 20 cm square.

at the time of entrance. He breathed more easily and had lost his appearance of anxiety, and percussion of the chest revealed that the tumor mass had become definitely reduced. After the fourth treatment, the respiratory excursions of the lungs were equal, and the breath sounds over the chest, anteriorly and posteriorly, were normal. An area of dulness extended 1 cm to the right and 2 cm to the

left of the sternum in the first and second interspaces anteriorly and to about 2 cm to either side of the upper thoracic part of the spine posteriorly. The heart was still displaced to the right. The roentgenograms showed that the left lung was entirely clear, except for a slight clouding at the cardiohepatic angle. The width of the mediastinal shadow was one half of that observed in the first roentgenogram (fig 8 B).

The patient was discharged with instructions to return in one month for a follow-up examination.

*Second Admission*—Thirteen days after discharge he was brought to the dispensary with a history of having been well until four days previously, when he began to be feverish and to have difficulty in breathing again. He had had recent nosebleeds, and blue spots had appeared in the skin. The mother had noticed an enlarging swelling on either side of the neck for three days.

On physical examination it was noted that the child was much thinner than at the time of the previous admission. Numerous petechiae and raised purpuric areas

TABLE 5—*Blood Picture in Case 2*

Date	Red Cells, Mil lions	Hemo globin, per Cent (Sahli)	White Cells	Platelets	Differential					Comment
					Lym pho cytes	Poly morpho nuclears	Mono cytes	Eosino phils	Baso phils	
9/ 1/31	5.22	96	17,400		23	77	0	0	0	
9/24/31	5.00	74	29,000	100,000	78	20	0	0	0	Coagulation time, 2.5 min, bleeding time, 15 min
9/25/31	3.41		34,000		70	21	7.5	2.5	0	Fragility test from 0.44 to 0.32
9/28/31	2.46	65	38,100		77	16	2.5	1.5	1	
10/ 1/31		42	38,700	10,000	82	11	3	1	0	
10/ 3/31	2.42	45	44,900		87	16	0	1	0	
10/ 9/31	1.90		18,300	40,000	82	18	0	0	0	
10/13/31	2.31	46	18,000		81	14	0	1	0	

from 1 to 2 cm in diameter, which were firm and tender to palpation, were scattered over the body. Small hemorrhages were present in the mucous membranes of the nose and mouth. The tonsils were swollen, edematous and necrotic. The cervical lymph nodes were enlarged, some of them being bean-sized and boggy, and others pea-sized and firm. The axillary, epitrochlear and inguinal glands were also the size of a small bean. No mass was found in the chest, and the lungs were clear. The heart was not displaced. The liver was not palpable. The spleen extended two fingerbreadths below the costal margin. Roentgen examination made at this time showed no increase in the mediastinal shadow, and the long bones were normal. The blood picture strongly suggested a leukemic process (table 5).

In view of the clinical history and physical findings, it was felt at this time that a diagnosis of a tumor of lymphatic origin, probably of the nature of a leukosarcoma, with a leukemic blood picture, could be made. It was thought probable that the roentgen therapy might have hastened the progress of the condition.

The subsequent course was typical of that of acute leukemia. The child had a temperature of from 101 to 101.4 F and almost constant hemorrhages from the nose and throat, and he grew rapidly weaker. The superficial lymph nodes, especially those in the cervical region, increased to the size of a hazelnut. The spleen did not enlarge further, however. The blood picture was that of progressive anemia with a lymphocytosis. Mitotic figures in the blast forms were seen, and

immature forms of granulocytes were also present. Before death the number of normoblasts increased decidedly. On the morning of October 13, there was profuse bleeding from the left tonsillar region. The patient became comatose and died. A permit for autopsy could not be obtained.

(This case is presented through the courtesy of Dr. Joseph Brennemann and Dr. Milo Pierce.)

#### COMMLN 1

The cases herein presented demonstrate that lymphosarcoma is a precursor of lymphatic leukemia. The peculiarity of these cases lies in the apparent effect of deep roentgen therapy on the development of the acute leukemic state and the final condition of the tissues at autopsy. It has been repeatedly shown by numerous investigators that the roentgen rays have an elective influence on the immature nuclei of rapidly multiplying cells. While this is clearly seen in these cases, as manifested by clinical improvement of the patients, there are evidences of other seriously deleterious effects on the hematopoietic and other vital organs. Some authors even think that this method of treatment accelerates the final outcome. In the cases presented at autopsy the bone marrow was found to be fatty, and the direct smears made from this marrow were quite cell-poor, indicating a state of aplasia. The kidneys showed interstitial infiltration with a mass of cells apparently with pyknotic and fragmenting nuclei, not associated with bacterial emboli. The very fact that the tissues of the various organs did not show typical lymphocytic infiltration may be explained on the basis of the far-reaching effect of deep roentgen therapy. The presence of numerous healing tubercles in some of the organs appears to be a mere coincidence. The bacterial emboli found in the lymph nodes are interpreted to be a secondary phenomenon due to granulocytopenia. Observations such as these compel us to raise a serious question as to the employment of roentgen rays in the treatment of this type of lymphosarcoma and leukemia.

Another important point in the proper evaluation of the condition studied is the sequence of events which in these patients led to terminal leukemia. The evidences seem to favor the belief that the lymphoblasts are first developed in a group of organs normally concerned in lymphopoiesis. Under certain stimuli, this process of lymphocytic differentiation is greatly accelerated, producing a pathologic hyperplasia of these organs. When the process is confined to the organs of primary involvement, the condition is lymphosarcoma or lymphoblastoma. When it extends to other organs belonging to the same system, by way of the lymphatics, it is designated as a metastasis. When this extension gets into the blood stream, it becomes leukemia. When the extension takes place into other organs not normally concerned with lymphopoiesis, such as the kidneys or the muscles, it is spoken of as a leukemic infiltration.

When both the organs and the blood show atypical proliferation, it is called by Steinberg leukosarcoma and by Pappenheim sarcoleukemia.

After the organs are infiltrated by the lymphoblasts the pathologic cells, possessed of abnormal power of multiplication, may cause a cellular hyperplasia, or the mere presence of the abnormal cells in these organs may set up a state of mesenchymal reaction, causing the undifferentiated cells of the mesenchyme to develop into lymphoblasts. In either event, the phenomenon is a true lymphoid metaplasia, or extralymphatic lymphopoiesis, analogous to the myeloid metaplasia often found in chronic myelogenous leukemia and in certain experimental conditions.

#### SUMMARY AND CONCLUSIONS

1. Two cases are reported in which the patients when first seen had lymphosarcoma with a normal blood picture, a short time later acute lymphatic leukemia developed with a rapidly fatal termination. This is additional evidence in favor of the view that lymphosarcoma and lymphatic leukemia are only different stages in the same pathologic process.

2. Roentgen therapy was instituted in both of these cases immediately after a diagnosis of lymphosarcoma was made and the question therefore arises as to whether or not this treatment induced the leukemic state.

# TOXICITY OF PURIFIED BILE PREPARATIONS

## III INFLUENCE ON CARDIOVASCULAR RESPONSES

FRED A RIES, M D

AND

EUGENE U STILL, Ph D

BALTIMORE

In a previous paper <sup>1</sup> we reported on the toxic effects of purified bile salts on the neuromuscular system. We found the neuromuscular junctions and reflex centers of the cord to be affected by small quantities of bile salts, whereas the skeletal muscle was relatively unaffected by similar amounts of the salts. We have investigated other nerve end-organs or junctions and reflex centers.

In 1905 Meltzer and Salant <sup>2</sup> first showed that the intravenous injection of bile increased the response to peripheral stimulation of the vagus in anesthetized rabbits. In some of their experiments stimuli which were subminimal became effective after the intravenous injection of bile. They did not determine the quantity of bile acids contained in the bile. However, the content was sufficient to cause a marked fall in the blood pressure. King and Stewart <sup>3</sup> suggested that the bradycardia frequently seen in chronic jaundice is due to the bile pigment. These workers claimed to have worked with bile pigment (bilirubin) in their experiments. However, since they gave no evidence of the purity of their preparation, we believe that it was contaminated with the toxic bile acids. This view is held since recent works proving the nontoxic nature of bilirubin have been published by Horrall, <sup>4</sup> Horrall and Carlson <sup>5</sup> and Still <sup>6</sup>. Buchbinder and Kern <sup>7</sup> reported experiments indicating that the threshold of nervous excitability is elevated in obstructive jaundice. Buchbinder <sup>8</sup> suggested that the bradycardia observed by him

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From the departments of physiology, the University of Chicago and the University of Maryland Medical School

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II Modification of the Parathyroid Tetany Mechanism in Jaundice, *Arch Int Med* **41** 754 (May) 1928

8 Buchbinder, W C. *Experimental Obstructive Jaundice* III Age Factor in the Production of Bradycardia, *Arch Int Med* **42** 743 (Nov) 1928

in jaundiced puppies (ligation of the common duct) was a specific reflex through the vagi

Most workers now agree that the toxicity of bile resides in the bile salts. However, recently Thomas<sup>9</sup> concluded that neither glycocholate nor taurocholate affects the cardiac rhythm, and that therefore neither could cause the bradycardia seen in jaundice.

Although some clinical investigators deny the co-existence of obstructive jaundice and bradycardia, others have observed that they are frequently associated. This work was undertaken in order to investigate the effect of purified bile salts on cardiovascular responses to nerve stimulation and some vasomotor reflexes. In these experiments we have used purified sodium cholate (Still<sup>6</sup>) and sodium dehydrocholate. Sodium dehydrocholate, which is of relatively low toxicity, was employed because the induction of changes in irritability was produced more gradually than with sodium cholate, and therefore the various stages could be followed with greater ease. The experiments were carried out on dogs, cats and rabbits under anesthesia produced by sodium barbital (275 mg per kilogram) or chloralose (8 mg per kilogram).

In most of the experiments the vagi were sectioned in the neck to exclude reflex cardiac inhibition. Mixed pressor-depressor responses were obtained by stimulation of the central end of the vagus nerve and the sciatic nerve. Cardiac inhibition was elicited by peripheral stimulation of the vagus nerve. In rabbits (with vagi intact) the same response was obtained by stimulation of the central end of the depressor nerve. The duration and intensity of the stimulating current were kept constant. Reflex pressor responses were elicited also by temporary occlusion of the carotid arteries. The responses of the sympathetic division of the autonomic system were studied by the injection of epinephrine hydrochloride solution.

#### STIMULATION OF NERVES

*Vagus Nerve Peripheral End*—Figure 1 shows the effect of intravenous injection of a small dose of the relatively nontoxic sodium dehydrocholate. It will be noted that stimulation of the peripheral end of the vagus nerve caused a greater and more prompt (shorter latent period) decrease in the blood pressure after the injection than in the control. If a larger amount of sodium dehydrocholate is injected in broken doses (total of 150 mg per kilogram) this period of hyper-irritability is followed by progressive decrease in response and finally by the development of a block. The block is a relative one, for increase

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<sup>9</sup> Thomas, E. *Rev. med. de la Suisse Rom.* 50: 207, 1930.



in the intensity of the stimulus produces a decrease in blood pressure comparable to that in the control

The intravenous injection of smaller doses of the more toxic sodium cholate (25 mg per kilogram) causes a shorter period of hyperirritability and a more rapid onset of depression and block. In most of our observations the decreased excitability affected the left vagus to a greater degree than the right one. If the sodium cholate is injected in small broken doses (total of 22 mg per kilogram), hyperirritability

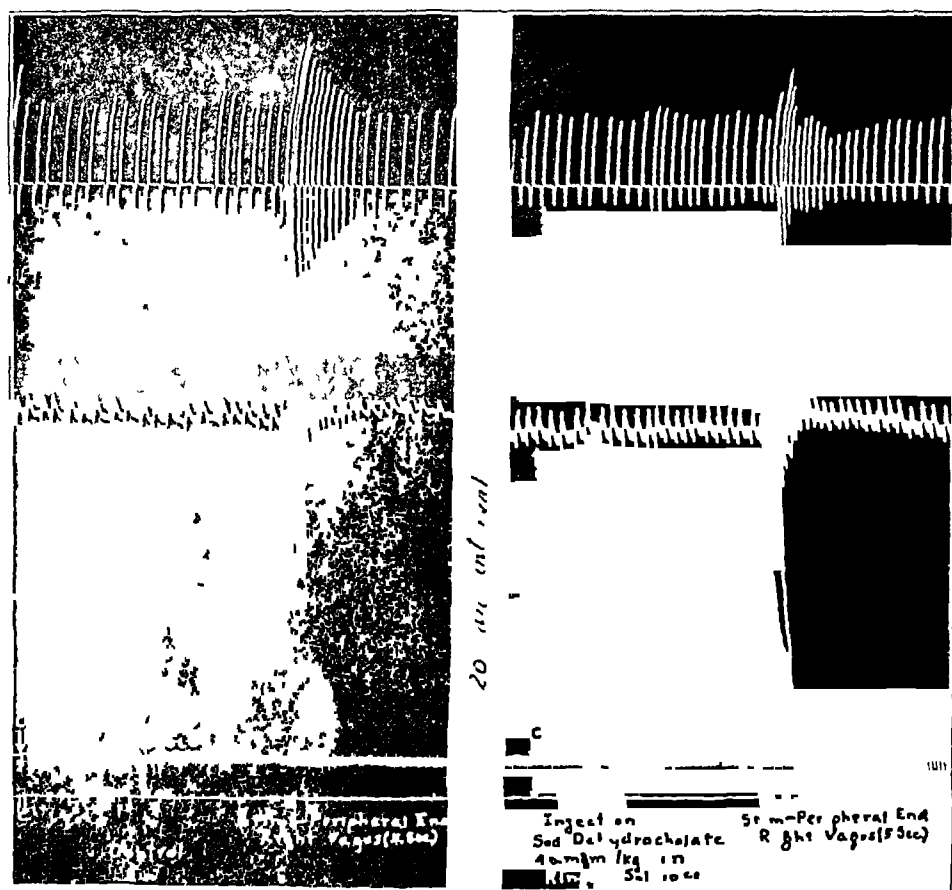


Fig 1—Tracings on a dog (barbital anesthesia, both vagi sectioned) Effect of peripheral stimulation of the vagus nerve before and after the injection of 40 mg of sodium dehydrocholate per kilogram intravenously

only may be encountered and may persist for an hour or longer after the first injection

It seems probable that the main influence is on the myoneural junction in the heart, because of the following facts 1 The local application of higher concentrations of bile salt than those used in these experiments apparently does not alter the conduction through the fibers of the vagus nerve. This is shown by the normal action currents and by the normal response of the heart to a stimulus applied at a point distal to a point on the vagus trunk where the bile salt was applied 2 Stimu-

lation of the central end of the vagus nerve produces marked reflex changes in blood pressure at a time when peripheral stimulation shows depression of irritability or block

*Vagus Nerve Central End*—Figure 2 shows the effect of stimulation of the central end of the right vagus nerve following the intravenous injection of a small dose of sodium cholate (17 mg per kilogram). It will be noted that three minutes after the injection stimulation caused a more prompt (shorter latent period) and a more marked pressor response than in the control, but after an interval of ten minutes there were a prolongation of the latent period and a marked decrease in the extent of the pressor phase with an increase in the depressor portion of the reflex. As shown in figure 3, following the

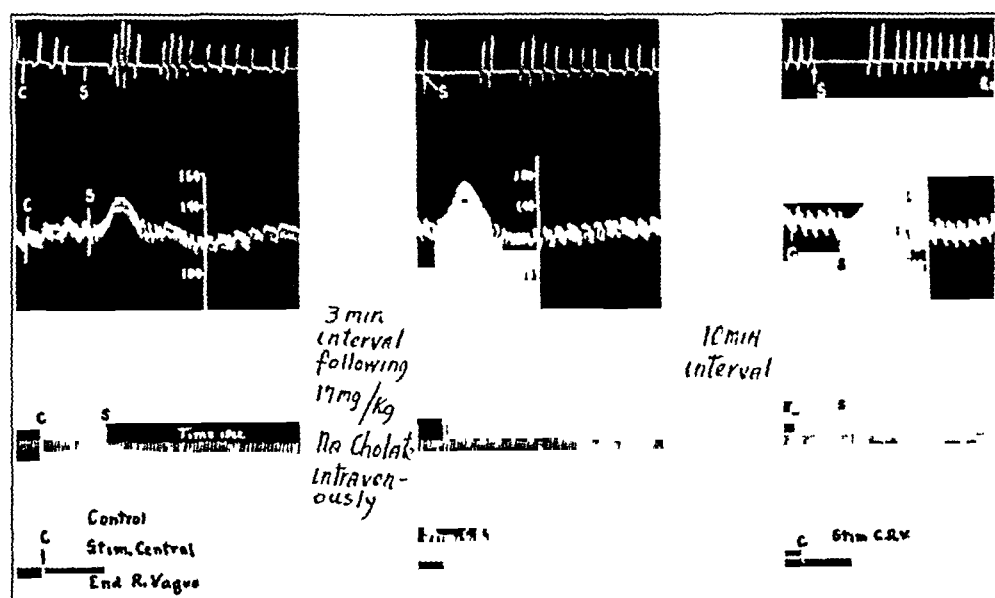


Fig 2—Tracings on a dog (barbitol anesthesia, both vagi sectioned) Effect of central stimulation of the vagus nerve before and after the injection of 17 mg of sodium cholate per kilogram intravenously

subsequent injection of sodium cholate (total of 37 mg per kilogram) there was absence of the pressor phase with only a depressor response. The vasomotor center was able to respond to anemia caused by increasing the intracranial pressure (introduction of warm saline solution under pressure).

In dogs in which a depressor response only was elicited on control stimulation of the central end of the vagus nerve, the injection of sodium dehydrocholate (40 mg per kilogram) caused this reflex decrease in blood pressure to become more marked and the duration of the latent period to be shortened.

We have recognized the fact that frequently one may obtain either pressor or depressor responses from central stimulation of the vagus and that the predominating response may alternate from one to the

other. However, in all of our experiments by this particular plan (ten) the response in every case was predominately depressor after the injection of bile salts, and in most of the cases the pressor phase was entirely absent.

*Depressor Nerve*—Following the administration of a small dose of sodium cholate or sodium dehydrocholate in rabbits there first appears a diminished response of the blood pressure to stimulation of the central

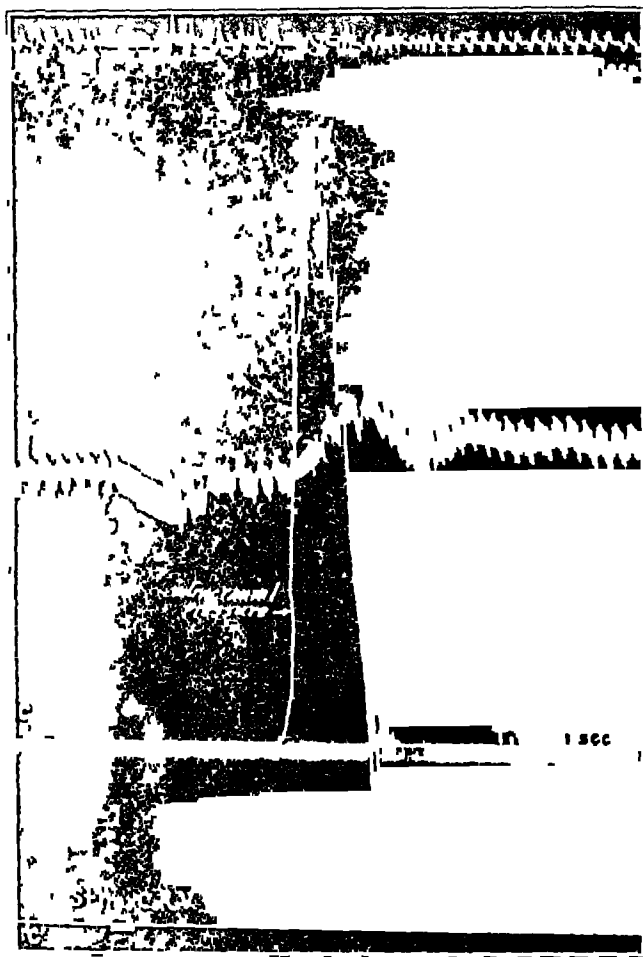


Fig 3—Tracings on the same dog as in figure 2 after a total of 37 mg of sodium cholate per kilogram had been injected intravenously in broken doses. For control see figure 2. On stimulation of the central end of the cut vagus nerve only the depressor phase was elicited. Raising of the intracranial pressure produced, however, a pressor response.

end of the depressor nerve. This is later followed by a period during which an augmented depressor effect may be obtained. We did not obtain a reversal of this reflex, as is frequently seen following the injection of ergotamine.

*Sciatic Nerve*—Following the intravenous injection of sodium dehydrocholate (50 mg per kilogram) the pressor effect on stimulation

of the central end of the sciatic nerve becomes more marked and may remain so for several hours. Figure 4 shows this increase in irritability. If one injects the more toxic sodium cholate (from 25 to 30 mg per kilogram), this period of hyperirritability is present but is soon followed by a decreased pressor response and then block. This is a relative block as a stronger stimulus will cause a response (as we found in the peripheral vagus experiments). We interpret this as indicating an increased threshold of the sympathetic synapses or endings.

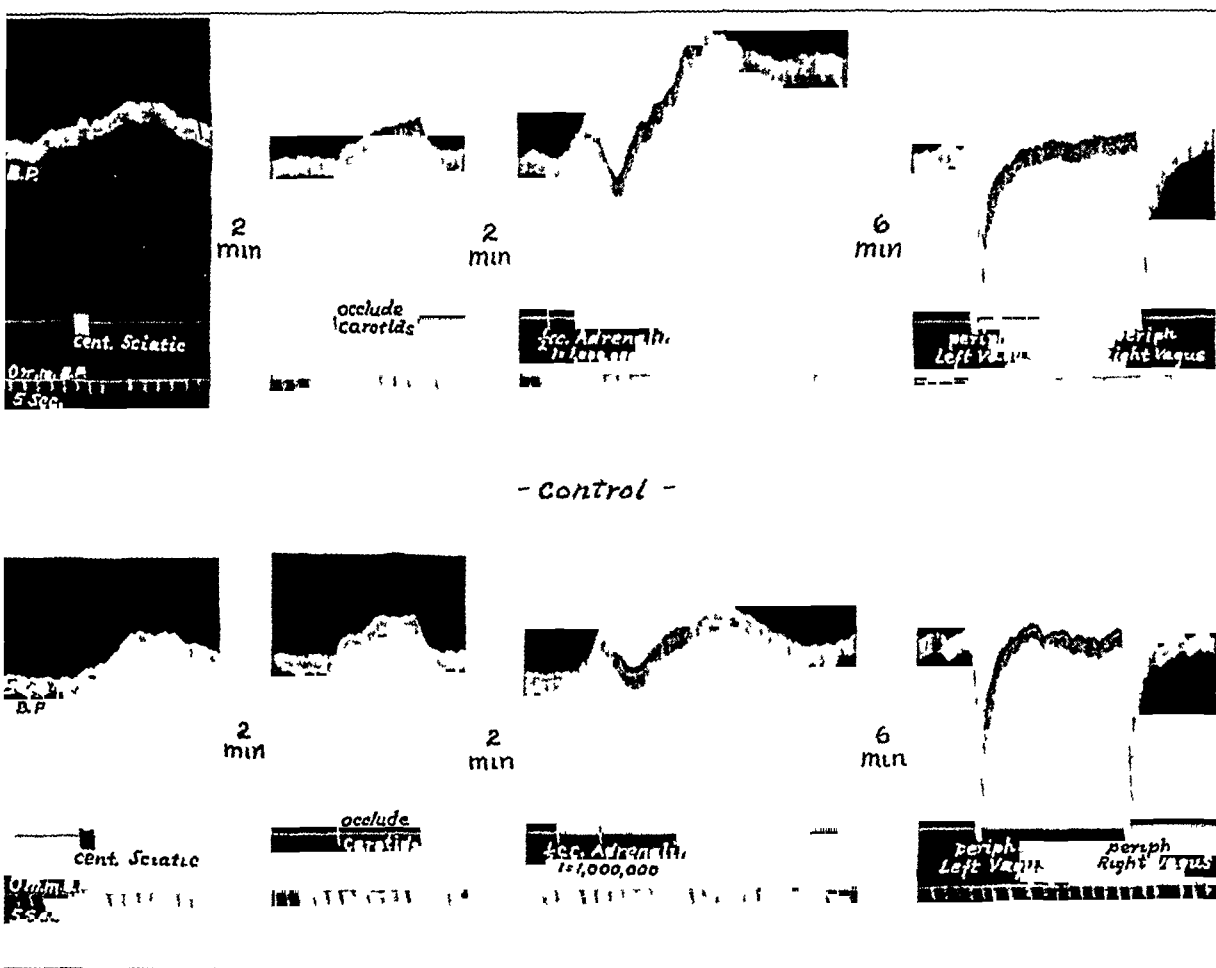


Fig 4—Tracings on a cat (chloralose anesthesia, both vagi sectioned). Blood pressure from femoral artery. Above control on the effect of stimulation of the sciatic nerve, occlusion of carotid arteries, intravenous injection of epinephrine and stimulation of the peripheral ends of the cut vagus nerves. Below control after the intravenous injection of 50 mg of sodium dehydrocholate per kilogram.

#### OCCLUSION OF THE CAROTID ARTERIES

The carotid reflex was elicited by temporary occlusion of the common carotid arteries. Figure 4 shows the effect on this response of the intravenous injection of 50 mg of sodium dehydrocholate per kilogram. Following the injection of the bile salt the reflex increase in blood pressure became slightly more marked than in the control. This hyper-

irritability persisted, though to a less marked degree, for two and one half hours after the injection. The intravenous injection of smaller doses of the more toxic sodium cholate (20 mg per kilogram) is followed by this persisting hyperirritable pressor reflex. In five of six experiments the pressor effect of occlusion of the carotids was more marked following the injection of bile salts than in the control, in the remaining experiment there was a primary period of decreased response followed by a pressor action greater than in the control. Large doses of bile salts were required to depress this reflex.

#### INJECTION OF EPINEPHRINE HYDROCHLORIDE

Luckhardt and Koppanyi<sup>10</sup> showed that when epinephrine is administered repeatedly at too short intervals there is a progressive decrease in its effects. Our epinephrine hydrochloride solutions were prepared just before use and kept in a chilled, stoppered container. The interval between the injections was at least fourteen minutes. We found in control experiments in which no bile salt was administered that the frequency and number of injections of epinephrine used by us did not fatigue the pressor mechanism.

Figure 4 shows the decrease in the response to intravenously administered epinephrine (0.5 cc of a 1:1,000,000 solution) after the intravenous injection of 50 mg of sodium dehydrocholate per kilogram. The duration, as well as the magnitude of the response, was decreased at a time when the vagal endings were shown to be hyperirritable. The pressor effect of epinephrine was still diminished two and a half hours after the injection of the bile salt. Similar results are obtained if one injects a small dose of the more toxic sodium cholate (from 20 to 25 mg per kilogram). In those experiments in which epinephrine gave primary and secondary pressor responses after the control injection, following the administration of bile salts in relatively large amounts, the same dose of epinephrine gave but one rise of decreased magnitude and duration. As a matter of fact, in all of our experiments doses of less than 100 mg of sodium cholate per kilogram obliterated the pressor response to epinephrine.

We did not observe a primary increase in irritability of the sympathetics as we did in the vagus and neuromuscular systems.

#### EFFECT OF INCREASED INTRACRANIAL PRESSURE

In order to determine the irritability of the central vasomotor mechanism after the injection of bile salts we produced anemia of the center

<sup>10</sup> Koppanyi, T., and Luckhardt, A. B. *Arch. internat. de pharmacodyn. et de therapie* **40**: 344, 1931. Luckhardt, A. B., and Koppanyi, T. *Am. J. Physiol.* **81**: 436, 1927.

by increasing the intracranial pressure (introduction of physiologic solution of sodium chloride under pressure into the cavity) The increased intracranial pressure was accompanied by a compensatory increase in blood pressure Figure 3 shows the effect at a time when only depressor responses were obtained by stimulation of the central end of the vagus nerve Moreover, asphyxia (clamping of the trachea) caused a marked pressor effect at a time when the pressor action of epinephrine hydrochloride or reflex pressor responses were greatly decreased or absent

#### COMMENT

Jenke and Steinberg<sup>11</sup> have reported that normal human blood contains 0.025 mg of bile salts per hundred cubic centimeters, while blood from icteric patients contains from 2 to 8 mg In our experiments we have injected from 10 to 40 mg of the salts per kilogram of body weight (in a few cases we have injected as much as 100 mg per kilogram) Assuming the circulating blood to be about 8 per cent of the body weight, we have caused an initial concentration of bile salts of from one to four times that found by Jenke and Steinberg in icteric patients Within a few minutes, however, the concentration would be reduced by dilution with the other body fluids to approximately 50 per cent of the initial concentration Our initial concentrations of blood are especially comparable to those found by Jenke and Steinberg when one considers our experiments with the less toxic salt, sodium dehydrocholate

Our experiments suggest that following the entrance into the circulation of small amounts of bile salts, there is a hyperexcitability of the vagus endings or junctions and depression of the vasoconstrictor endings This removal of the antagonistic influence of the sympathetic endings would permit vagal predominance and may account for the bradycardia noted by Buchbinder<sup>6</sup> during the early stages of obstructive jaundice in puppies We believe that the diminished response to epinephrine was due mainly to depression of the vasoconstrictor endings or junctions In three experiments in which the vagi were cut, the change in amplitude and rate of the pulse following the intravenous injection of epinephrine was about the same before and after the injection of the bile salts If the bile salts affected mainly the cardiac muscle, as is supposed by Buchbinder, one would expect the cardiac response to epinephrine to be different in the two cases

The later progressive decrease in vagus irritability and the introduction of a relative block at the vagal endings or junctions due to the toxic action of bile salts suggest an explanation for the periods of relative and absolute tachycardia noted by Buchbinder in the puppies

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<sup>11</sup> Jenke and Steinberg Arch f exper Path u Pharmacol **153** 244, 1930  
Jenke ibid **163** 175, 1931

following the primary bradycardia. The possibility remains, however, that the lower blood calcium (Andrews, Rewbridge and Hrdina,<sup>12</sup> and Buchbinder and Kern<sup>13</sup>) may play a rôle in the production of tachycardia late in obstructive jaundice. The tachycardia may be of other than sinus origin. It is interesting to note that Buchbinder and Kern reported variation in pulse rate in frogs following obstruction of the common duct. These phenomena would partially account for the hypotension noted in obstructive jaundice, other factors being myocardial involvement, gastro-intestinal disturbance and malnutrition. The tendency toward hypotension may be partly counteracted by a reflex involving the carotid sinus, as indicated from our experiments, for rather large amounts of bile salts are required to depress this reflex.

In the experiments with intact vagi we have not detected significant changes in the pulse following the injection of bile salts because of the diminution or absence of vagus tone in anesthetized animals.

It is our opinion that an important factor in the development of bradycardia observed clinically is the increased sensitivity of the vagus endings (or junctions) and the decreased sensitivity of the sympathetic endings (or junctions). This opinion is further supported by the recent work of Jenke and Steinberg on the concentration of bile salts in normal and icteric men.

In the doses employed in these experiments only the large amounts of bile salts affected the toxic discharge of the vasomotor center. Small amounts of bile salts at first decrease the latent period and increase the extent of the reflex pressor responses. Larger amounts of bile salts (or a more toxic salt) prolong the latent period and alter the extent of the vascular reflexes at a time when the vasomotor mechanism can react readily to anemia. This suggests that the alteration occurs in the region of the efferent side of the center.

#### CONCLUSIONS

These experiments seem to warrant the following conclusions as to the site of action and the effect of purified bile salts on cardiovascular response:

- 1 Bile salts do not materially affect conduction through nerve fibers.

- 2 Small concentrations of bile salts increase the irritability of the vagal endings or junctions, and the same amounts decrease the sensitivity of the vasoconstrictor endings or junctions.

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<sup>12</sup> Andrews, E., Rewbridge, A. G., and Hrdina, L. S. *Proc. Soc. Exper. Biol. & Med.* **27** 755, 1930.

<sup>13</sup> Buchbinder, W. C., and Kern, R. *Am. J. Physiol.* **80** 273, 1927.

3 The injection of large doses of bile salts tends to produce block (relative or absolute) of the endings of both systems

4 These factors are probably involved in the production of the changes in the pulse rate noted in obstructive jaundice

5 The medullary centers are more resistant to bile salts than are their peripheral components



# SPLENECTOMY IN SICKLE CELL ANEMIA

REPORT OF A CASE WITH NECROPSY IN AN ADULT ON WHOM  
SPLENECTOMY WAS ATTEMPTED

R E CHING, M D

AND

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MEMPHIS, TENN

The physician faced with the care of a patient with severe sickle cell anemia, with its characteristic hemolytic jaundice, recurrent attacks of pains in the muscles and joints abdominal symptoms, ulcers of the legs, fever and increased susceptibility to intercurrent infections, is likely, after the usual antianemic measures have failed, to give serious consideration to any procedure which offers hope of benefit Splenectomy,<sup>1</sup> first suggested by Sydenstricker on the basis of the similarity of the disease to congenital hemolytic icterus has been given a prominent place in the literature as a means of treatment The results of the removal of the spleen have been reported in seven instances<sup>2</sup> All the splenectomies have been performed on children The trend of opinion in regard to the procedure is optimistic, and one is likely to be impressed by the enthusiastic claims for surgical cure The negative or unfavorable results and contraindications are not so obvious unless a critical analysis of the recorded data is made

It was our unfortunate experience to have advised splenectomy on a young adult with active sickle cell anemia At operation no spleen

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From the Department of Pathology, Pathological Institute, University of Tennessee

1 Sydenstricker, V P Sickle Cell Anemia, South M J **17** 177 (March) 1924

2 (a) Hahn, E V, and Gillespie, E B Sickle Cell Anemia Report of a Case Greatly Improved by Splenectomy Experimental Study of Sickle Cell Formation, Arch Int Med **39** 233 (Feb) 1927 (b) Stewart, W B Sickle Cell Anemia Report of a Case with Splenectomy, Am J Dis Child **34** 72 (July) 1927 (c) Bell, A J, Kotte, R H, Mitchell, A G, Cooley, T B, and Lee, Pearl Sickle Cell Anemia Report of Two Cases in Young Children in which Splenectomy was Performed, Am J Dis Child **34** 923 (Dec) 1927 (d) Hahn, E V Sickle-Cell (Drepanocytic) Anemia, with Report of a Second Case Successfully Treated by Splenectomy and Further Observations on the Mechanism of Sickle-Cell Formation, Am J M Sc **175** 206 (Feb) 1928 (e) Landon, J F, and Lyman, A V Sickle Cell Anemia with Case Report of Splenectomy, Am J M Sc **178** 223 (Aug) 1929 (f) Levy, F E, and Schnabel, T G Abdominal Crises in Sickle Cell Anemia, Am J M Sc **183** 381 (March) 1932

was found, and the patient died. In order that others may avoid our mistake, the case is reported. Evidence for or against splenectomy is weighed, and the essential pathology of the disease is emphasized. Further justification of this paper lies in the fact that extensive clinical and hematologic studies were made over a two year period, and a complete autopsy was performed.

#### REPORT OF A CASE

*History*—A. L. C., aged 18 years, an unmarried Negress from Mississippi, was observed at frequent intervals in the outpatient department of the Memphis General Hospital, and on four occasions was admitted to the wards. The early history is fragmentary, as the patient was illegitimately born and from early infancy lived with relatives. Nothing is known concerning the health of the father, but the mother worked regularly, had no history of anemia and did not possess the sickle cell trait.

At school and while working in the cotton fields, the patient tired more easily than other children and took little part in their play. The diseases of childhood were not followed by complications, and there were no serious illnesses. Sore throats, colds, digestive disturbances and pains in the joints were frequent. During childhood she often had "cat boils," a chronic type of ulceration which heals slowly, and which is said to be common among Negroes on plantations. At the age of 14, a large ulcer appeared on the anterior of the right leg, just above the ankle, which did not heal for a year.

When 16 years of age, the patient obtained employment as a nurse maid, but found the work heavy and was unable to keep a position because of attacks of sickness in which symptoms in the joints and abdomen were prominent.

*Examination*—In March, 1928, at the age of 18, she reported to the outpatient department with the complaint of menorrhagia associated with fever, epistaxis, abdominal pain and leukorrhea. Physical examination revealed a tall, slender girl, of average intelligence, appearing younger than her given age with a prominent forehead, scanty pubic and axillary hair and poorly developed external genitalia. Other findings of importance were jaundice, pallor, tonsillar hypertrophy, general enlargement of the lymph glands, a nontransmitted systolic murmur, low blood pressure, hepatomegaly, infantile uterus, edema of the ankles and round, depressed scars of numerous ulcers on the shins of both legs. The lungs were clear, and the spleen not palpable. Cervical smears were negative for gonococci. The Wassermann reaction was 4 plus. The gallbladder was not visualized by the Graham test. Intramuscular treatment with mercury salicylate was instituted. There was no improvement.

In May, 1928, she was admitted to the gynecologic ward with the diagnosis of an acute condition of the abdomen, the symptoms of which were severe pain in the lower part of the abdomen, nausea and vomiting. The temperature was 103 F., and there was marked abdominal tenderness. The leukocyte count was 28,000, the erythrocyte count, 2,800,000, and the hemoglobin, 20 per cent (Sahli). There was definite jaundice, with an icteric index of 42. A flat plate failed to reveal gallstones. Cultures of the blood and stool gave negative results. The acute symptoms subsided within a few days, and the general condition gradually improved. She was discharged at the end of two months, with the diagnosis of "acute salpingitis, syphilis and cholecystitis with jaundice." Sickle cell anemia was not suspected.

During the next year she "just ailed around" and became extremely weak. An unproductive cough developed, and she began to have night sweats. She lost 55 pounds (24.9 Kg). The menses became irregular and scanty, and were often accompanied by pain in the lower quadrant and epistaxis. Episodes of severe pains in the muscles and joints were frequent. Nocturia developed.

In April, 1929, an injection of mercuric salicylate was followed by stomatitis and an exaggeration of the abdominal symptoms. She was admitted to the medical service and remained under observation for two months. The physical findings were unchanged.

An examination of the blood which was made on this admission revealed a severe hemolytic anemia with evidence of active regeneration. The values for the red

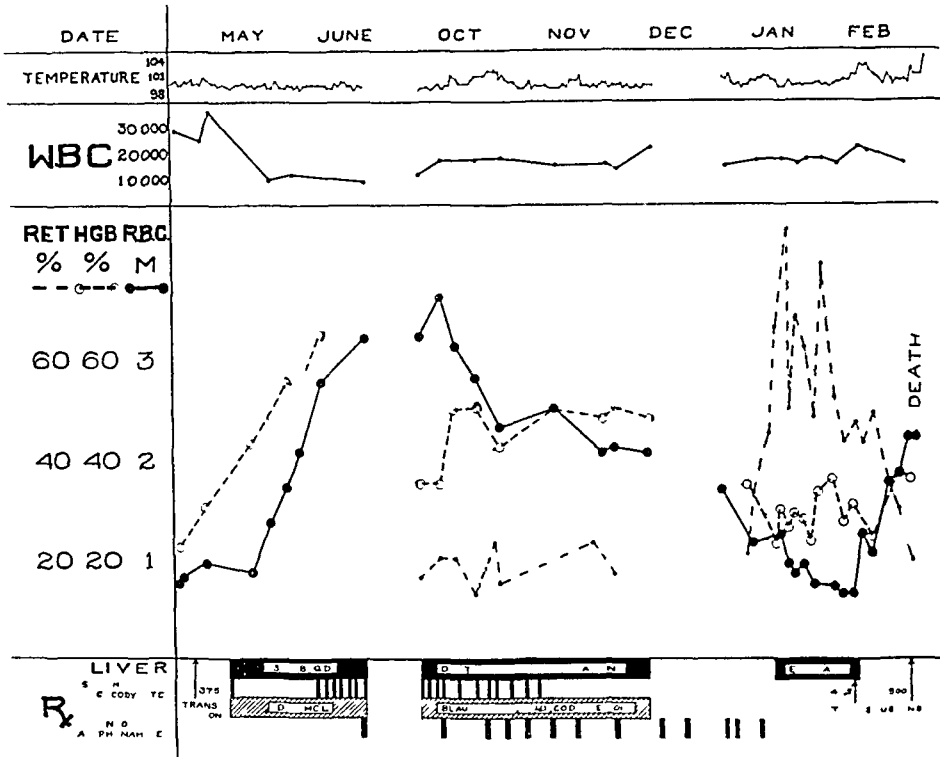


Fig 1—Chart showing temperature and the values in leukocytes, erythrocytes, hemoglobin and reticulocytes in relation to therapy

and white blood cell counts, hemoglobin and reticulocytes for this and subsequent admissions are given in figure 1. The color index was variable. The volume of packed red blood cells was 23 cc per hundred cubic centimeters of whole blood. The mean corpuscular volume was 73 cubic microns, the mean corpuscular hemoglobin, 27 micromicrograms, and the mean corpuscular hemoglobin concentration, 37 per cent. When a drop of blood was sealed under a coverslip and examined immediately, only occasional pointed erythrocytes were noted. On standing, the bizarre and spiked red cells rapidly appeared, reaching a maximum of from 80 to 100 per cent in from eighteen to thirty hours. The erythrocytes readily became sickle cells in brilliant cresyl blue preparations, and it was noted that the mature cells without reticulum showed a higher percentage of sickle cells than did the heavily reticulated cells (fig 2). The pointed rod and slender crescent forms so numerous and typical in the stained smears in some cases of sickle cell anemia in this case were difficult to find. Constant features of the dry smear preparations were anisocytosis, aniso-

chromia, moderate poikilocytosis, diffuse basophilia, Jolly's bodies, megaloblasts, nucleated red blood cells and numerous platelets. Mitotic megaloblasts, stippled cells and phagocytosis of erythrocytes by large mononuclear cells were observed, but were infrequent.

Leukocytosis was constant. The differential formula showed an increase in the immature granulocytes, and a normal percentage of polymorphonuclears with four and five lobes. The eosinophils were not increased on the first two admissions, but later averaged 10 per cent. The average mononuclear percentage was 3.

The platelets were consistently increased, and were often large and well preserved. The bleeding time was seven minutes. The coagulation time (capillary pipet method) was one and one-half minutes. The clot was firm and retracted well. The fragility test revealed beginning hemolysis at 0.36 per cent of sodium chloride, and complete hemolysis at 0.24 per cent of sodium chloride.

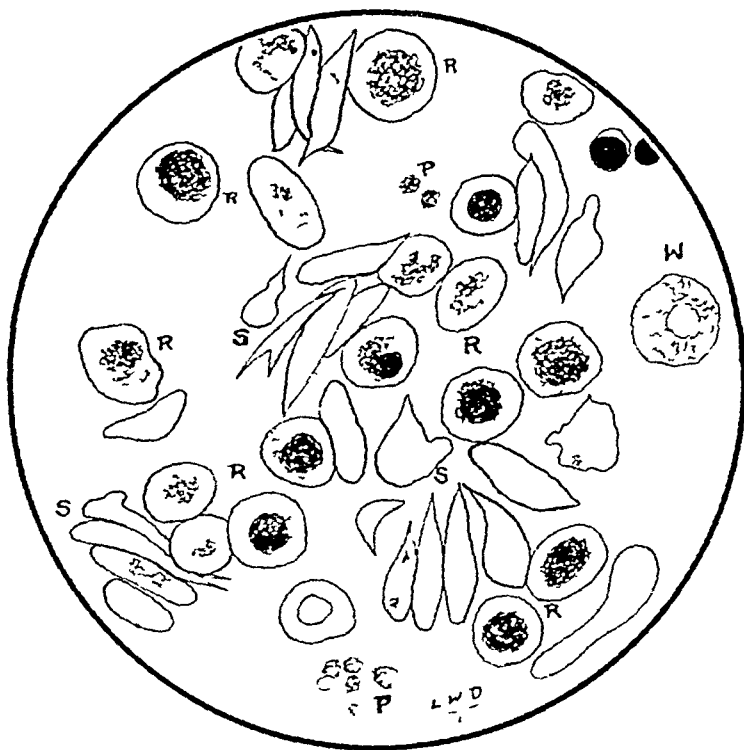


Fig 2—Moist, brilliant cresyl-blue preparation. Drawing of an actual oil immersion field, showing numerous reticulated erythrocytes, most of which are nucleated. The nonreticulated cells sickle to a greater degree than those containing a great amount of dye. R, reticulated red blood cells, S, sickled red blood cells, W, degenerated leukocyte, and P, platelets.

The urine showed urobilin, traces of albumin, occasional hyaline and finely granular casts, and a few red blood cells. The phenolsulphonphthalein test yielded a 35 per cent excretion in the first hour and a 25 per cent excretion in the second. The nonprotein nitrogen was from 24 to 30 mg per hundred cubic centimeters of blood, and the creatinine, 14 mg. No free hydrochloric acid was found in the gastric contents before or after the test meal. Blood cultures were negative. A roentgenogram of the chest showed slight left ventricular hypertrophy.

*Treatment*—Following a transfusion of 375 cc of whole blood the patient was placed on a diet of liver, and in addition given sodium cacodylate, dilute hydrochloric acid, and mercury and iodide tablets. The clinical condition slowly

improved. There was a steady increase in the erythrocytes and hemoglobin, and a decrease in leukocytes (fig 1). During this stay in the hospital there were low grade intermittent fever and occasional attacks of abdominal pain. The patient was discharged in July, 1929.



Fig 3—Spleen, increased amount of connective tissue containing black staining, calcareous material. Reduced from a magnification of  $\times 200$ .

During the remainder of the summer the patient was unable to continue on a regular diet of liver, her varied symptoms continued, and in September of the same year she was again admitted. The findings were essentially the same as on previous admissions. The red cell count was 3,200,000, and the hemoglobin, 35

per cent (Sahli) Jaundice persisted, the icteric indexes varied from 25 to 50 The stools were dark brown, and there was urobilinuria Gastric analysis again revealed an absence of free hydrochloric acid The temperature remained elevated, and sweating was profuse Abdominal pains, distress after eating and nausea were often complained of Epistaxis occurred on two occasions Headaches were frequent There were three attacks of severe pain in the joints and backache, lasting from two to five days Partial relief was obtained by the use of salicylates and hot applications The attacks disappeared without leaving residual soreness or limitation of movement In one attack there were severe pain and stiffness of the

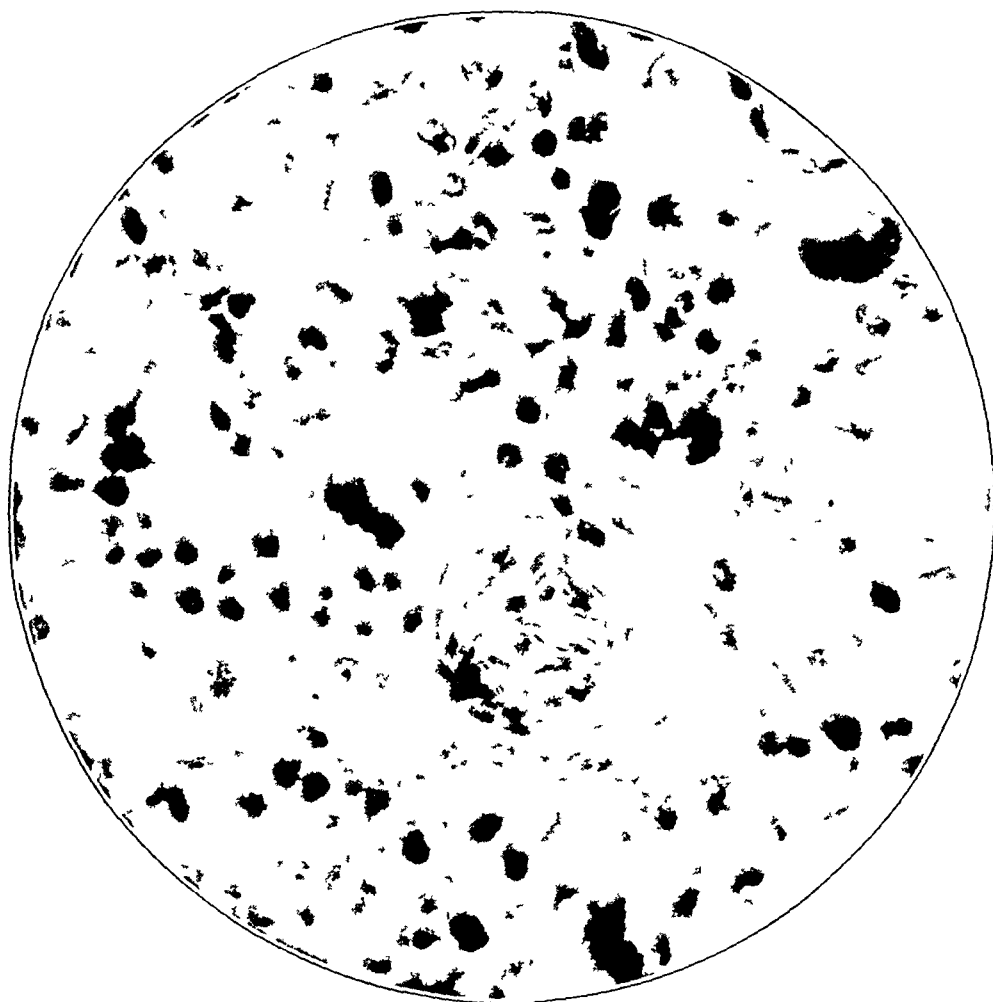


Fig 4—Bone marrow, general hyperplasia and clumps of sickle erythrocytes resembling agglutinated corpuscles Magnification,  $\times 750$

left arm, and the wrist was definitely swollen and hot At another time the patient complained of pain in both wrists, and later of backache and immobility of the left thigh The therapy and progress of the anemia are shown in figure 1 A striking change in the blood picture at this time was the development of marked eosinophilia and a diminution in the number of nucleated red blood cells The general condition remained unaltered, but the patient was allowed to go home

Seventeen days after discharge she was back in the hospital, with the complaint of stiffness in the right arm and left leg, severe pain in the left upper quadrant and "shaking chills" The left ankle and right wrist were swollen, with a local

increase in temperature. There was a profuse vaginal discharge. The symptoms and signs of anemia were more severe, the systolic murmur more pronounced and the liver larger.

On this admission the blood picture was that of a most striking regeneration, with numerous premature cells of the erythrocytic and myeloid series present. On Jan 14, 1930, the percentage of reticulocytes reached 87, and nucleated red blood cells outnumbered the leukocytes. Following the administration of liver extract, 3 ampules a day, the reticulocytes decreased somewhat, but the erythrocytes continued to fall, and the hemoglobin did not significantly change. Peculiarly, the icteric index figures were lower than on previous admissions, being 9 and 19.

In view of the tendency of the anemia and clinical symptoms to become progressively worse, in spite of intensive therapeutic measures, splenectomy was con-

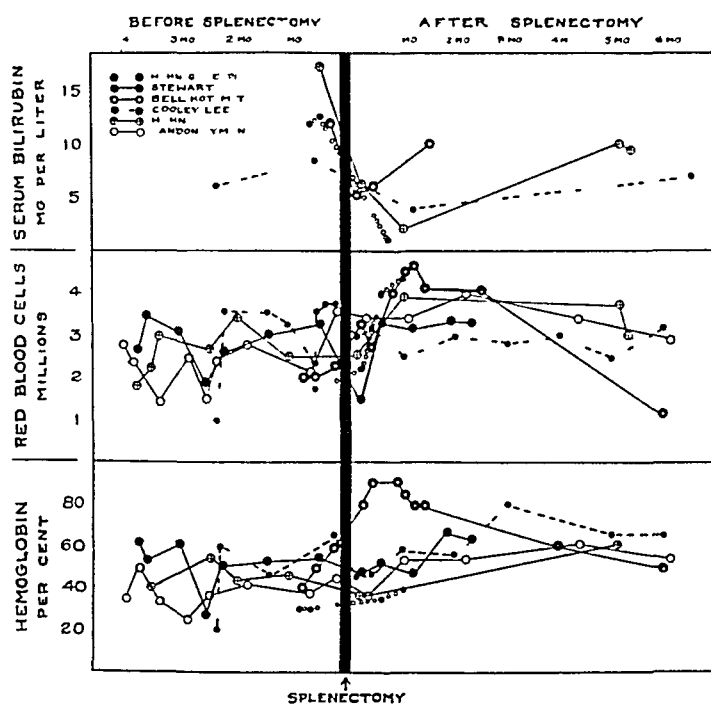


Fig 5—Chart showing results of splenectomy in sickle cell anemia. Preoperative and postoperative values in serum bilirubin, red cells and hemoglobin in six reported splenectomies.

sidered the only remaining hope. A preoperative transfusion was given, but a tonsillar abscess developed, and the operation was withheld until it subsided. Another transfusion was given, and an exploratory laparotomy was done by Dr McGehee through a left rectus incision. The spleen could not be found. Following the operation, the patient's condition became critical, and death occurred on the next day.

**Autopsy—Gross Findings.** Autopsy was performed within an hour after death. All tissues were deeply icteric. The serous cavities contained a slight excess of clear, yellow fluid. There were many adhesions about the gallbladder, in the region of the spleen and in both pleural cavities.

The heart weighed 250 Gm and was devoid of gross abnormalities. The middle lobe of the right lung was studded with numerous tubercles. The bronchial glands were large and caseous.

The liver weighed 2,210 Gm, it was of average consistency and rust brown. Each kidney weighed 200 Gm and was of a color similar to that of the liver. The gallbladder was thin-walled and contained no stones. The bile ducts were patent.

What proved to be the spleen was a tiny, nodular unit lying flat against the diaphragm and deeply buried in dense adhesions. It weighed 10.5 Gm and was very firm. The dark red pulp was partitioned into many small units by yellowish scars.

The retroverted uterus measured 5 by 2.5 by 2 cm. The tubes and ovaries were small. There were no pelvic adhesions.

There was general enlargement of the lymph glands, the largest measuring from 1 to 2 cm in diameter. With the exception of the bronchial glands, all the glands were discrete, brown and soft.

The aorta was thin and elastic. The intima was smooth.

The skull was thickened, the greatest dimensions (2 cm) being in the parietal regions. The inner surface of the shaft of the femur was irregular and penetrated in a few places by soft red marrow. The marrow of the femur, ribs and vertebrae was red and semifluid.

The other organs showed nothing noteworthy.

Bacteriologic studies of the heart's blood, bone marrow and spleen revealed no organisms on smear or culture.

**Microscopic Findings** The studies of the tissues were made on material fixed in a solution of formaldehyde, embedded in celloidin and stained with hematoxylin-eosin.

In every tissue most of the erythrocytes were uniformly greatly elongated and fusiform.

Sections from the middle lobe of the right lung showed many miliary and conglomerate tubercles, especially around the larger bronchi and blood vessels. There was little caseation or encapsulation. The bronchial lymph glands showed large areas of caseation bordered by giant cells and epithelioid cells.

There was a small amount of perivascular infiltration of the round cells in the adventitia of the aorta, but no intimal or medial changes could be made out.

The blood capillaries of the liver were widely distended with sickle cells, which in many instances were clumped in large, round masses suggesting agglutination. The Kupffer cells were enormously increased in number and size, and frequently contained from three to six nuclei. They were laden with varying amounts of ingested sickle cells and pigment granules. As many as from 20 to 30 sickle cells were frequently seen within a single phagocyte. The polygonal cells exhibited a heavy deposit of amorphous brown pigment, concentrated more in certain areas, but lacking a zonal distribution. There was a heavy infiltration of the periportal spaces with small round cells, plasma cells, eosinophils and large mononuclears. A few epithelioid tubercles were found in every section.

The capsule, trabeculae and pulp of the spleen showed a great amount of scarring. Black-staining, slender, beaded threads parallel to the connective tissue fibers and concentrated in the vessel walls were a striking feature (fig 3). After decalcification this material was no longer perceptible. In the capsule and the trabeculae were a few large, black and green staining granules, which on decalcification took a pink stain and resembled grains of starch. Some of these granules were within the cytoplasm of foreign body giant cells. In one of the trabeculae was a large, round, granular, red-staining body, with a thick capsule, resembling an *Aspergillus* head.



The pulp mostly consisted of extensive extravasations of sickle cells. The pulp cords were congested, the malpighian bodies were inconspicuous and fibrosed. Much of the pulp was extremely cellular, and showed numerous megalokaryocytes, plasma cells, small round cells, macrophages, polymorphonuclears and eosinophils. There were also a few islands of large, pale-staining, round cells (myelocytes?). No normoblasts could be recognized. All of the arteries and arterioles showed a thickened intima owing to proliferation of large, pale, vacuolated endothelial cells. Many of the lumens were obliterated. A few vessels showed breaks in their walls, which were infiltrated by round cells, plasma cells and fibroblasts.

The glomerular capillaries in the kidneys were engorged with sickle cells and capsular spaces filled with fat droplets and a granular, brown-staining material. Many convoluted tubules showed hyaline droplet degeneration. Everywhere the tubular epithelium contained numerous small, brown, amorphous, pigment granules, most marked in the convoluted portions. The collecting tubules contained hyaline, granular and fatty casts. There were a few small round cells in the interstices.

No fat could be found in the bone marrow. The marrow was rich in nucleated cells. Erythroblastic and leukoblastic islands were numerous. Polymorphonuclear neutrophils, eosinophils, pigment-laden macrophages and megalokaryocytes were present in large numbers. There were large clumps of small round cells resembling lymphocytes. Dispersed throughout the marrow there were numerous large, round cells, with pale, vesicular nuclei containing nucleoli, and having varying amounts of cytoplasm. With the Wright stain these cells were of an unclassifiable, primitive type. The sickle cells were as abundant in the reticular spaces as in the blood vessels. In many instances they were closely packed into large round masses, resembling the clumps found in the liver (fig 4). There were a few large areas of hemoglobin which corresponded in size to the clumps of sickle cells.

The medulla of the lymph glands was distended with numerous large mononuclears, plasma cells, lymphocytes, pigment-laden macrophages and many other cells which could not be identified. No hemolymph glands were found.

In summary, the pathologic findings were jaundice, anemia, atrophy of the spleen with fibrosis and infiltration of calcium, hepatomegaly, hyperplasia of the bone marrow, thickening of the skull and irregularities in the cortex of the femur, general hyperplasia of the lymph glands and chronic mediastinal and terminal miliary tuberculosis.

#### COMMENT

The clinical, hematologic and autopsy observations reported in this case are characteristic of sickle cell anemia. Striking hematologic features are the extremely high counts for reticulocytes, the scarcity of sickle cells in the stained smears and the inconstant eosinophilia. No conclusions can be drawn as to the effect of liver or other therapy, because too many antianemic measures were concurrently employed and the disease was complicated by syphilis and tuberculosis. Syphilis must be considered as a possible explanation of the indolent ulcers of the legs. In retrospect it is obvious that the continuation of neoarsphenamine in the presence of continued fever and progressive anemia was ill advised (fig 1).

The symptoms and signs of sickle cell anemia are often suggestive of a pathologic condition which requires surgical intervention, and it is of interest that this patient was first admitted to the gynecologic service.

an acute condition of the abdomen being suspected. The clinical diagnosis of pelvic inflammatory disease was not confirmed by autopsy. On this first admission there was also an entire lack of appreciation of the factor of hemolysis in the production of the jaundice.

The inability of the surgeon to find the spleen at operation was readily explained at autopsy, for the fibrotic remnant was flattened out and so firmly adherent to the diaphragm that it appeared as part of it. The possibility of encountering a spleen too small to be removed should have been anticipated, because such is the characteristic finding in adult patients with sickle cell anemia. Sydenstricker<sup>3</sup> also attempted to perform splenectomy on an adult in whom the atrophic spleen was estimated to measure 6 by 4 cm. Bennett,<sup>4</sup> Jaffe,<sup>5</sup> Sydenstricker and others<sup>6</sup> and Steinberg<sup>7</sup> reported autopsies in which the spleen was as minute as in our case. That the spleen may undergo complete obliteration in active sickle cell anemia was shown in a recent autopsy on a man aged 51, in whom no remnant of splenic tissue could be found.

Splenomegaly has frequently been found in young children, and by many it is thought to be characteristic of the early stages of the disease. The essential feature of the pathologic condition of the spleen, according to Rich,<sup>8</sup> is congestion of the pulp, present in all in whom the sickle cells occur. In the active anemic state, this engorgement is extreme, and there may be hemorrhages and infarcts. Fibrosis follows, varying with the amount and duration of injury, and leads to shrinkage. Whether splenomegaly is always a characteristic early manifestation and whether fibrosis with atrophy always follows remains to be proved. Stewart<sup>2b</sup> noted progressive enlargement of the spleen followed by atrophy in a child with successive anemic episodes. Much more data must be available before any definite conclusions can be drawn concerning the pathologic condition of the spleen in this disease.

#### SPLENECTOMY IN SICKLE CELL ANEMIA

Recorded opinion as to the value of splenectomy in sickle cell anemia is divided. Hahn<sup>2d</sup> stated that profound anemia is an indication rather

3 Sydenstricker, V. P. Further Observations on Sickle Cell Anemia, *J. A. M. A.* **83** 12 (July 5) 1924.

4 Bennett, G. A. Sickle Cell Anemia. Further Investigation of a Case of Splenic Atrophy with Calcium and Iron Incrustations (Nodular Splenic Atrophy), *Arch. Path.* **7** 801 (May) 1929.

5 Jaffe, R. H. Die Sichelzellenanämie, *Virchows Arch. f. path. Anat.* **265** 452, 1927.

6 Sydenstricker, V. P., Mulherin, W. A., and Houseal, R. W. Sickle Cell Anemia. Two Cases, One with Necropsy, *Am. J. Dis. Child.* **26** 132 (Aug.) 1923.

7 Steinberg, B. Sickle Cell Anemia, *Arch. Path.* **9** 876 (April) 1930.

8 Rich, A. R. The Splenic Lesion in Sickle Cell Anemia, *Bull. Johns Hopkins Hosp.* **43** 398 (Dec.) 1928.

than a contraindication for the procedure, and that it is irrational to withhold operation in cases in which the spleen is not palpable Sydenstricker<sup>9</sup> expressed his opinion thus "The benefit derived from the operation has varied directly with the size of the spleen, where there was marked splenomegaly improvement has been considerable, where the spleen was small, the results have been discouraging" Musser and Wintrobe,<sup>10</sup> stated that "this method of treatment is still in the experimental state Improvement has been noted, particularly in those infants in whom splenomegaly was present" Yater and Mollari<sup>11</sup> advocated splenectomy in active cases as early as possible

Graham and McCarthy,<sup>12</sup> Steinberg,<sup>7</sup> and Leivy and Schnabel<sup>21</sup> in recent publications stated that there is little favorable evidence for splenectomy, and that whatever improvement has followed has at best been only temporary The effects of splenectomy on hemolysis and anemia as revealed by the values in serum bilirubin, erythrocytes and hemoglobin are summarized in graphic form (fig 5) Leivy and Schnabel's case is omitted because the postoperative data were not published, an entire lack of improvement, however, being noted In Hahn and Gillespie's case it is possible that there was permanent improvement, but the postoperative follow-up was only of one month's duration In the cases of Bell and others, Cooley and Lee, and Hahn, there was temporary improvement of varying degree and duration, but in Bell's case there was a severe remission at the end of six months In Stewart's case, the only one in the series in which there was a small spleen, the patient was not benefited by the procedure, nor was Landon and Lyman's patient, in whom the removed spleen weighed 640 Gm (in a 6 year old child) All cases which were followed for as long as two months after operation showed no striking improvement, on the contrary, the fluctuations in the erythrocyte counts and hemoglobin continued as in active sickle cell anemia In addition, no constant or significant changes were noted in the leukocytes, nucleated red blood cells, reticulocytes or fragility, and in no case was there a permanent alteration in the sickle cell trait

Clinical improvement was noted in three cases<sup>13</sup> In three cases the abdominal crises recurred<sup>14</sup> There was no operative mortality

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9 Sydenstricker, V P, in Christian, H A Oxford Medicine, New York, Oxford University Press, 1930, vol 2, p 849

10 Musser, J H, and Wintrobe, M M, in Tice Practice of Medicine, Hagerstown, Md, W F Prior Company, 1931, vol 6, p 844

11 Yater, W M, and Mollari, M The Pathology of Sickle Cell Anemia Report of a Case with Death During an Abdominal Crisis, J A M A **96** 1671 (May 16) 1931

12 Graham, G S, and McCarthy, Sarah H Sickle Cell (Mensisocytic) Anemia, South M J **23** 598 (July) 1930

13 Footnote 2a, c and d

14 Footnote 2b, e and f

It is manifest that the cases have been too few, the age group too limited and the preoperative and postoperative data too meager to allow a fair appraisal of the procedure. In the interpretations of the results as recorded, the effects of other therapeutic measures, such as transfusion and hospital care, have not been given due consideration. More important still is the fact that spontaneous remissions are characteristic of sickle cell anemia. In the case reported in this article there was definite clinical and hematologic improvement on the first two admissions.

On the basis of the recorded evidence, it is our opinion that the benefits of splenectomy have not yet been proved. If the procedure is to be given further trial, it should be on an experimental basis, and attempted only in cases in which the spleen is enlarged. The removal of small spleens may not only be valueless, but it may be, as in our case, impossible, and may impose on the patient an additional operative risk. In all cases of adults and of some children with active sickle cell anemia in which autopsy observations have been reported the spleen has been small.

#### SUMMARY AND CONCLUSIONS

1 A case of active sickle cell anemia is reported in an adult on whom splenectomy was attempted, a complete autopsy was performed.

2 An analysis of the literature in regard to splenectomy reveals that permanent benefit following the procedures has not been proved.

3 The fibrosis and atrophy of the spleen in chronic cases of sickle cell anemia establish a definite contraindication for splenectomy in adults.

Mr Joseph L. Scianni, artist, Pathological Institute, University of Tennessee, made the photomicrographs.

# NOURISHMENT OF THE MYOCARDIUM THROUGH THEBESIAN VESSELS

IN A HEART IN WHICH THE LARGE CORONARY ARTERIES AND VEINS  
WERE DESTROYED BY TUBERCULOUS MYOCARDITIS

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Interest in the thebesian vessels or sinusoids has been renewed to a considerable degree in recent years. Pratt,<sup>1</sup> Kretz,<sup>2</sup> and Wearn,<sup>3</sup> particularly, have studied these vessels, and have expressed the belief that the heart can be effectively nourished through these channels after both coronary arteries have been occluded. Leary and Wearn<sup>4</sup> further believe that under such conditions the only source of blood supply to the myocardium is through these channels.

Although several instances of occlusion of both coronary arteries have been reported<sup>5</sup> in which a thebesian circulation was assumed, in no such case, so far as we know, have the sinusoids or dilated thebesian channels been investigated histologically and their distribution and other features studied. The heart of a boy, aged 16, described in case 5 in a paper on "Tuberculosis of the Myocardium,"<sup>6</sup> presented a certain combination of pathologic changes which make it appear that for a period, at least, the main body of the ventricles was nourished solely by the thebesian vessels. We wish to present the pathologic and histologic evidences on which this opinion is based.

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From the Division of Cardiology and Pathology of the Philadelphia General Hospital and the Robinette Foundation of the University of Pennsylvania.

1 Pratt, J. H. The Nutrition of the Heart Through the Vessels of Thebesius and the Coronary Veins, *Am J Physiol* **1** 92, 1898.

2 Kretz, J. Ueber die Bedeutung der Venae minimae thebesii fur die Blutversorgung des Herzmuskels, *Virchows Arch f path Anat* **266** 647, 1927.

3 Wearn, J. T. The Role of the Thebesian Vessels in the Circulation of the Heart, *J Exper Med* **47** 293, 1928.

4 Leary, T., and Wearn, J. T. Two Cases of Complete Occlusion of Both Coronary Orifices, *Am Heart J* **5** 412, 1930.

5 (a) Albutt, Clifford. Diseases of the Heart, Including Angina Pectoris, London, The Macmillan Company, 1915, vol. 2, p. 21. (b) Batson, O. V., and Bellet, S. The Reversal of Flow in the Cardiac Veins, *Am Heart J* **6** 206, 1930. (c) Cabot, R. C., and Mallory. Case 16061. Pain Between the Thyroid and Xyphoid, *New England J Med* **202** 287, 1930. (d) Leary and Wearn.<sup>4</sup>

The large coronary arteries were completely occluded a short distance from their origin by tuberculous intimal involvement and by compression from a surrounding caseous tumor.<sup>6</sup> The medium-sized arteries were also destroyed.<sup>7</sup> Occasional arterioles near the endocardium were found to be patent, but so far as we could determine the destruction proximally of the larger arteries prevented these small arterioles from receiving blood through the usual channels. The large veins were affected to an even greater degree than were the arteries, the surface vessels being entirely destroyed. In the inner half of the myocardium where caseation had not destroyed them, large dilated veins with thickened walls were found. The coronary sinus and the main vein leading to it were considerably dilated over a distance of  $\frac{3}{4}$  of an inch (1.9 cm). At this point, however, the vein became entirely occluded by the tuberculous process, there being therefore, no way for the blood to enter or to leave the right auricle through the coronary veins.

In this heart, therefore, a condition existed in which at best only the auricular muscle and a small portion of the ventricular muscle could have received any blood through arteries. Moreover, reversal of blood flow through the coronary sinus and veins, a mechanism which Batson and Bellet<sup>8</sup> believe under certain circumstances may be important in the nourishment of the myocardium, could not have been active, at least in the final stages, because of destruction of the main coronary veins and the closure of the coronary sinus. It is difficult, therefore to avoid the conclusion that the undestroyed ventricular muscle in this case, in its terminal stages at least, received its nutrition entirely through a thebesian circulation.

#### PATHOLOGIC OBSERVATIONS

The heart was exhaustively studied by means of serial section made from various portions. Sections from the ventricles showed the right ventricle to be relatively less involved by tuberculosis than the left, the walls of the latter being almost entirely caseous except for a narrow subendocardial zone, where the myocardium had been preserved.

The wall of the right ventricle contained an amazing number of vascular spaces or sinusoidal channels, relatively few were present in the muscle of the left ventricle (compare figures 1 to 6 with figure 7). The sinusoidal spaces near the endocardium were on the whole more

6 Gouley, B. A., Bellet, S., and McMillan, T. M. Tuberculosis of the Myocardium. A Report of Six Cases with Observations on Tuberculous Involvement of the Coronary Arteries, *Arch. Int. Med.*, to be published.

7 The auricular coronary branches arising from the proximal undestroyed portions of the coronary arteries were patent.

8 Batson and Bellet.<sup>5d</sup>

numerous and larger than those deep in the muscle. Their walls likewise were thicker and more highly organized, being composed of a relatively thick outer fibrous wall, lined by endothelium, while the smaller intramural ramifications often possessed a wall of no more than a single layer of endothelium.

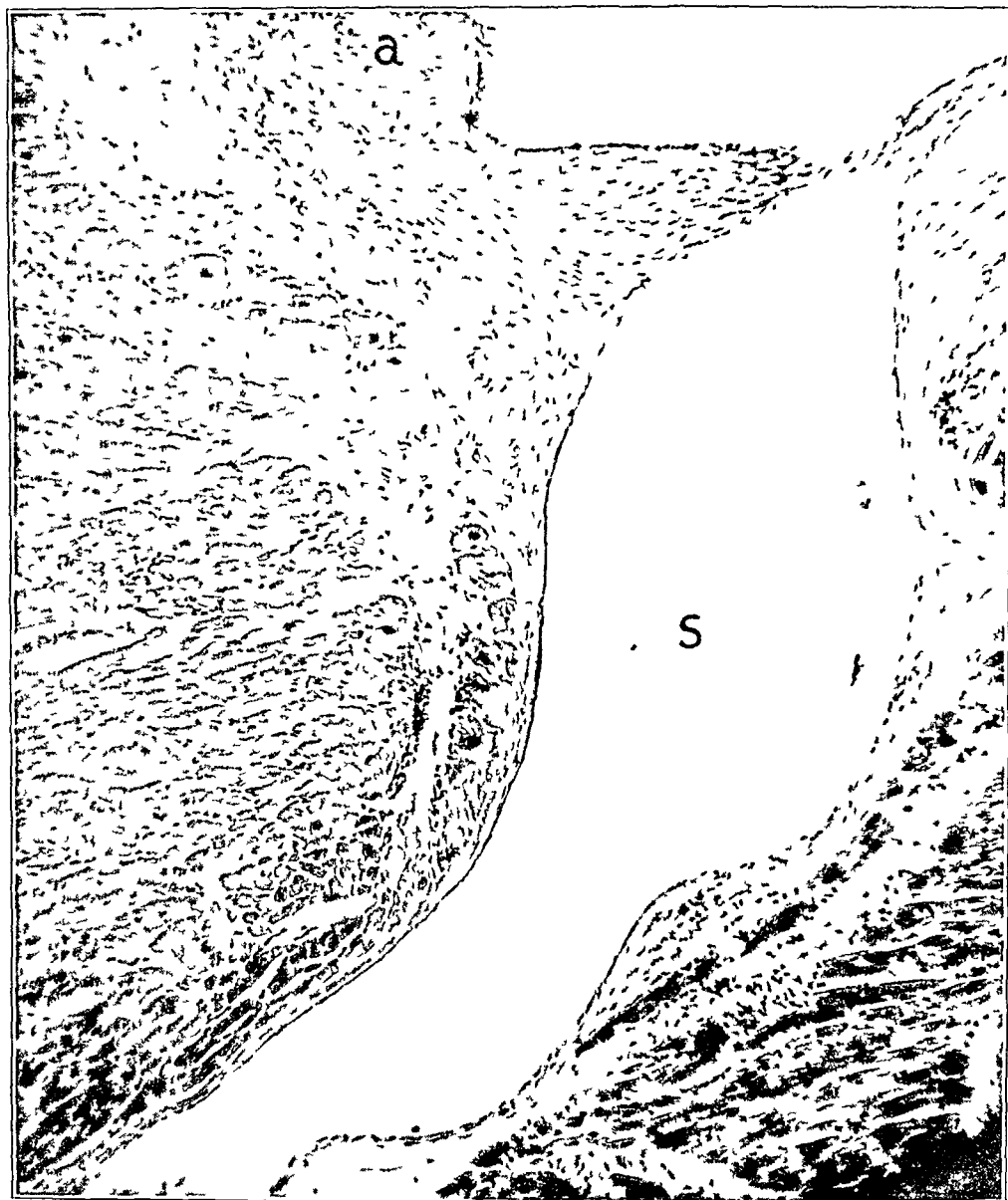


Fig 1—Sinusoid within the myocardium. Large saccular sinusoid (*S*) with irregular fibrous thickening of the wall. Part of this thickening (*a*) may be due to tuberculous infiltration,  $\times 60$ .

The diminution in size of these vessels as they penetrated the interior of the muscle was not always a gradual or progressive change, sinusoids frequently maintaining the caliber of larger medium-sized veins until they became united with such vessels. Not infrequently,

large sinusoids with fibrous walls suddenly became narrowed, giving the appearance of sacculation, beyond this constriction the channels often showed sudden increase in size, leading to one or more thin-walled spaces, this formation suggested that the latter thin-walled dilatation may at times have exercised a sort of reservoir function and acted to retain blood within the myocardium during certain phases of the cardiac cycle, the narrowing and sacculation aiding by exercising a sort of valvular mechanism (fig 1)



Fig 2—Low power view of a large dilated vein (*V*) and numerous sinusoids (*S*) branching into the myocardium. Their connections with veins (*V*) were traced by serial sections,  $\times 30$

These thin-walled sinusoidal vessels could be traced from the endocardium to the larger veins in the depth of the cardiac muscle, with which they communicated directly and freely. On the other hand, communication with the arterial system was difficult to follow. Capillaries leading from some of the smaller arterioles could be traced to the sinusoids, but only after a comparatively long and tortuous course. This makes us unwilling to say that the occasional undestroyed arteriole may not have participated to some extent in the circulation.



We are certain, however, that in the end-stages they were not connected with large arteries, and that their only connection was with sinusoids by means of infrequent small tortuous capillaries, which we do not believe were sufficient to furnish an effective amount of blood to the undestroyed arterioles. That these remaining arterioles did not function efficiently is also indicated by the fact that in many of them remnants of endothelial debris could be seen. In figure 6, an



Fig 3—Dilated thin-walled sinusoids (*S*) in the depth of the myocardium. These can be traced to a large subendocardial sinusoid and to the vein seen in figure 2. Note the obliterated artery (*A*),  $\times 57$ .

arteriothebesian connection is shown, the relative size of the capillary connection can be judged by comparing it with the arteriole and sinusoid shown.

The differentiation between veins and large sinusoids was often difficult and sometimes impossible. When the fibrous walls contained some remnant of smooth muscle, the identification was simple. In a number of instances, a gradual transition from vein to sinusoid was present, what appeared to be a vein in one section could be classed as a sinusoid in the next. In one section, illustrated in figure 5, the

wall of the vessel shows the histologic evidence of a vein in one segment and a sinusoid in the rest of the circumference. Red blood cells were observed in many of the sinusoids.

Elastic tissue stains (Weigert) brought out the surprising fact that the normally small amount of elastic tissue observed in the venous walls was continued throughout the anastomoses and transitions until the endocardium was reached. Large thin-walled spaces under the

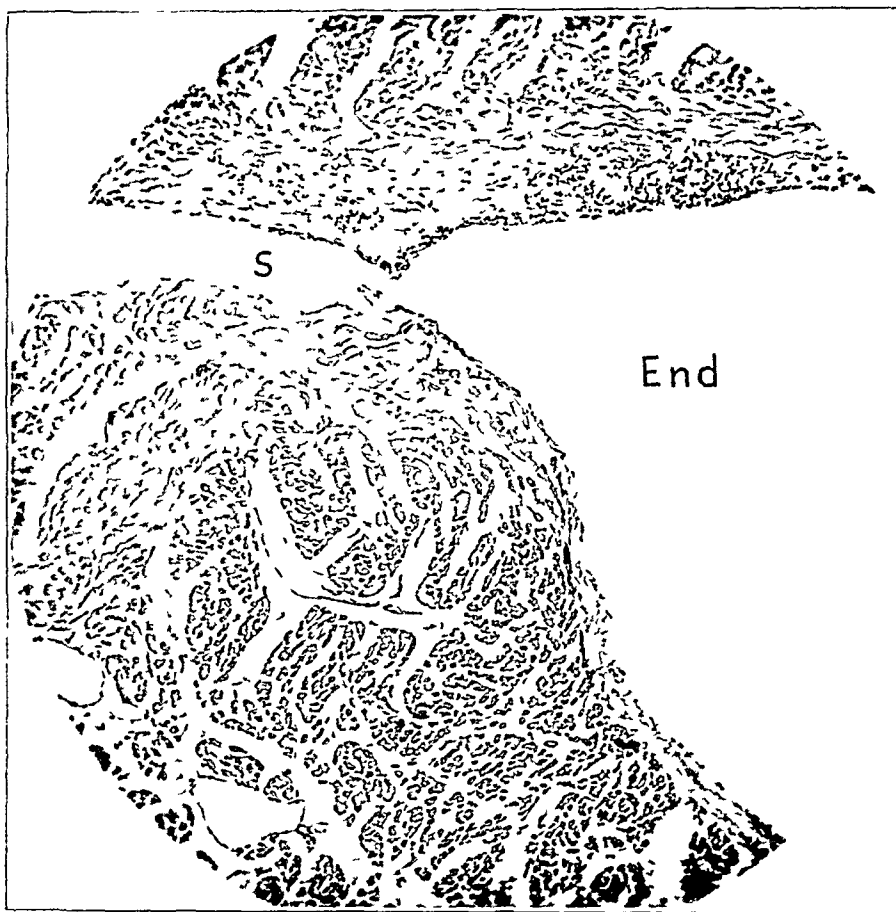


Fig 4—The opening of a sinusoid (*S*) into the endocardium (*End*). Note the endocardial thickening with a cribriform constriction at the mouth of the sinusoid,  $\times 62$ .

myocardium and also the so-called “communicating pits” contained thin strands of elastic tissue.

#### COMMENT

It should be recalled that at least from one half to two thirds of the right, and three fourths of the outer portion of the left, ventricular wall were destroyed by the caseous process. A sinusoidovenous circulation sufficiently nourished this small portion of the ventricular wall to support life for a relatively considerable period. How efficiently such a system would have maintained a circulation in ventricular walls

of normal thickness is not shown by our case. The relatively few sinusoids in the remaining left ventricular wall in a heart in which this system was developed most probably to a maximum make it somewhat difficult to see how a left ventricular wall of normal thickness could be adequately nourished by such a mechanism alone. In this connection it should be remembered that the thebesian vessels were more numerous subendocardially and progressively became smaller and less numerous toward the outer portions of the ventricular walls.

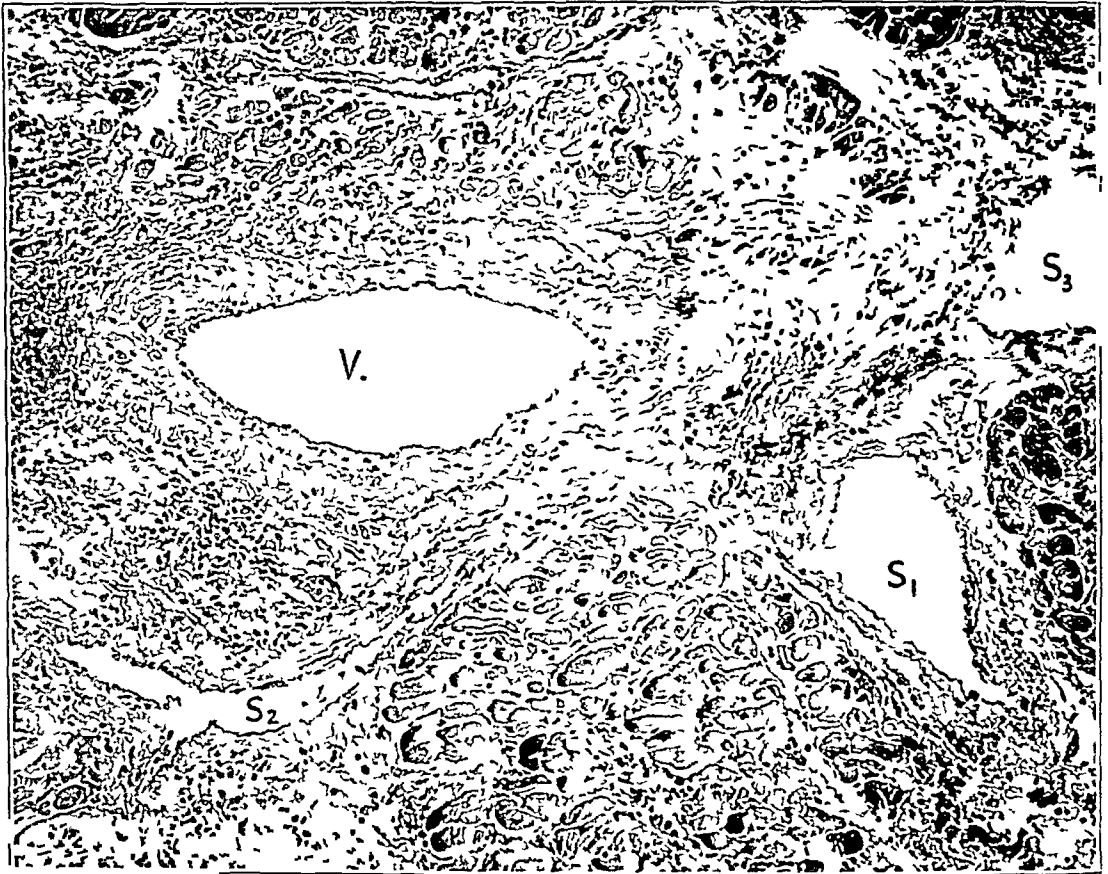


Fig 5—A vein (*V*) with a number of branching sinusoids (*S*<sub>1</sub>, *S*<sub>2</sub> and *S*<sub>3</sub>). The venous wall contains definite smooth muscle structure, whereas the sinusoids do not, except *S*<sub>1</sub>, which shows the transition from the venous to the sinusoid formation, a segment of its wall is thicker, contains an occasional smooth muscle nucleus and merges directly with the vein at a slightly lower level,  $\times 100$

This fact suggests that before its destruction by tuberculosis, the outer left ventricular wall had a system of thebesian vessels inadequate to its circulatory needs. Circulatory insufficiency, therefore, may have been a factor in the disproportionately greater destruction of the left ventricular myocardium.

*The Mechanism of the Dilatation of the Thebesian Vessels*—Three possible factors may have played a rôle in the dilatation of these

potential thebesian channels (1) intraventricular tension, (2) intra-auricular tension or (3) intra-arterial tension. Any discussion of the rôle of these factors must be regarded as hypothetic. We wish, however, to discuss the possible part played by the intra-arterial pressure, because we have certain direct pathologic evidence which suggests that this was an important, if not the primary, means by which these channels became dilated. Of the vessels affected by the tuberculous process, the surface veins apparently suffered first. This seems probable because of the thinness of their walls and the comparatively lower pressure in

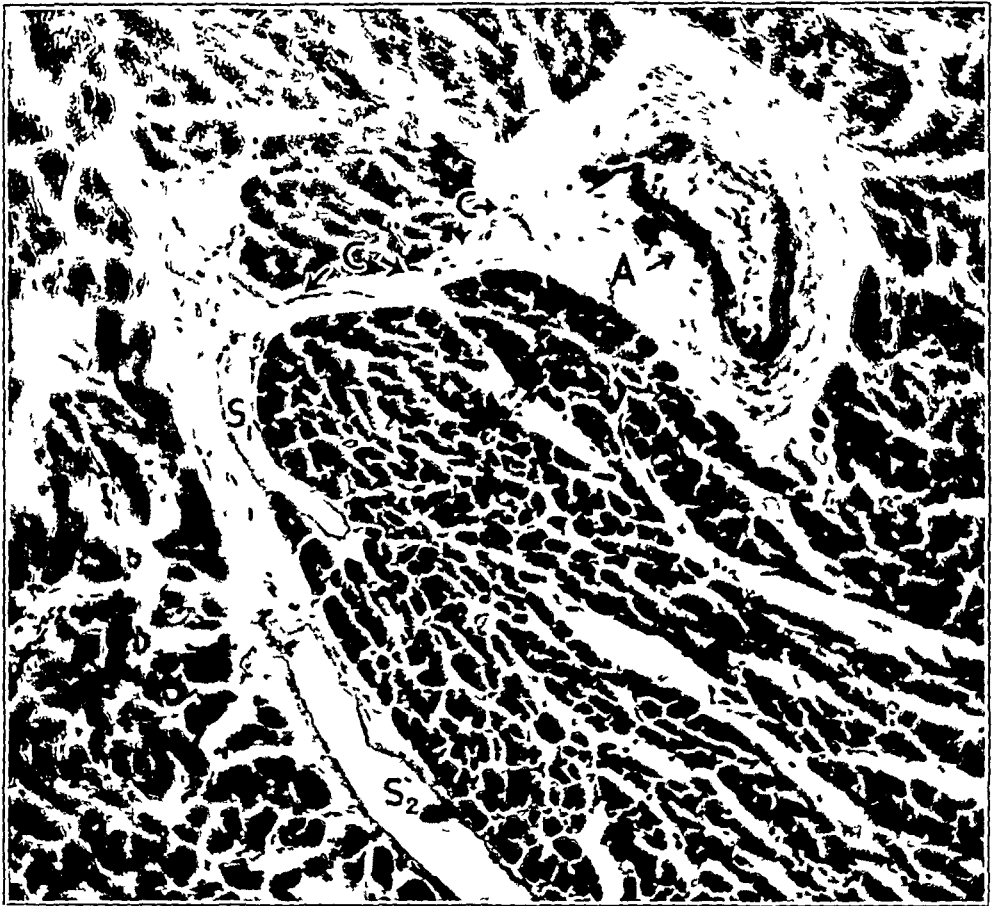


Fig 6—Arteriolar-sinusoid communication via capillary (*c*). *S*<sub>2</sub> leads directly to the endocardium. Such communications were only by means of capillaries,  $\times 100$

the venous system, and also because of the fact that although the proximal portion of the great surface arteries were occasionally observed, the accompanying veins were found to have been completely destroyed. With closure of the surface veins and, later, of the coronary sinus, the arterial blood was forced to seek new channels of egress, the only other outlets being thebesian vessels emptying into the right auricle and right ventricle and, to a lesser extent, into the left ventricle. The portion of the intramural venous system as yet not

engulfed in the process of caseation was under increasing pressure, the vessels constantly enlarging to accommodate the diverted venous blood. Later, after complete closure of the large coronary arteries and reduction of the coronary arterial pressure to practically zero, these dilated sinusoidovenous channels served as the only means of nourishing the myocardium. Leaving aside theoretical considerations of the manner of the original dilatation of these channels, intraventricular

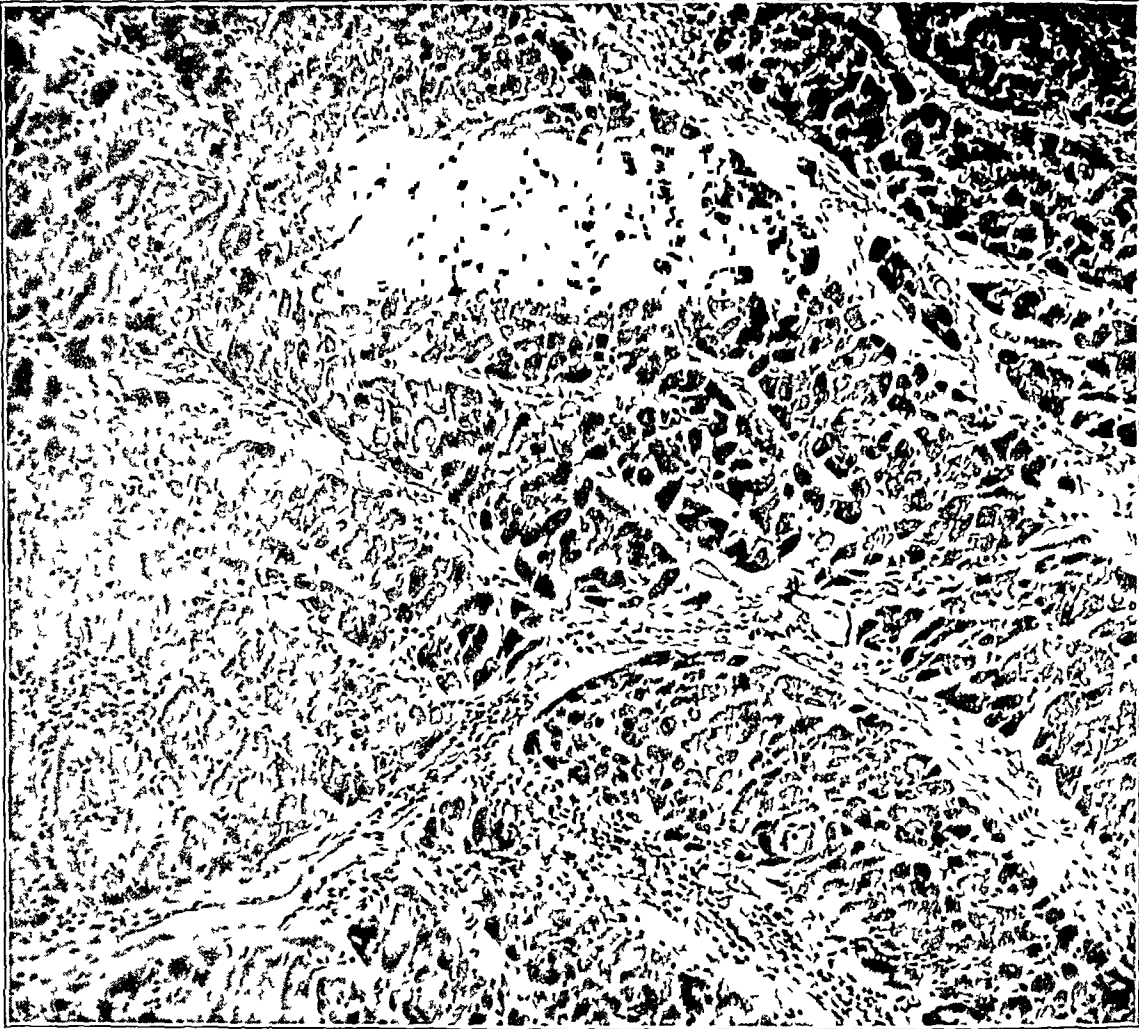


Fig 7—A section from the narrow zone of the remaining intact myocardium of the tuberculous left ventricle, tuberculous sinusoids, while present, are relatively few as compared with the numbers seen in the previous photographs taken from the right ventricular sections,  $\times 100$

tension was sufficient to maintain a circulation through these dilated sinusoidovenous channels after the pathologic changes were fully developed. We believe that the circulation occurred by an ebb-and-flow effect. Our case furnishes no data as to whether blood entered the myocardium during diastole or during systole.

*Arteriothebesian Anastomoses*—Wearn<sup>9</sup> expressed the belief that there exist relatively large and free connections between arteries and thebesian vessels. This belief has not been confirmed by the injection and histologic studies of Grant and Viko,<sup>9</sup> nor by the work of Stella,<sup>10</sup> who employed physiologic methods. In the case we describe, there undoubtedly were arteriothebesian connections. These however, were infrequent and were of no higher order than small capillaries, the arterial side of this connection was never larger than a small arteriole (fig 6). It seems unlikely, therefore, that the thebesian-arterial connections were a potent factor in the nourishment of this heart.

#### CONCLUSIONS

The heart of a 16 year old boy is described in which an unusual degree of tuberculous fibrocaseous infiltration had destroyed the coronary arteries and the large surface veins. A system of sinusoids (thebesian vessels) many of which were dilated and some of which had thickened walls connected the endocardium with remaining intramural veins and furnished the only means of myocardial nourishment.

The unusual pathologic cause of the obliteration of the coronary circulation (both arteries and veins) prevents a direct and exact comparison of the circulatory features of the heart described with those seen in double coronary occlusion of the more chronic types.

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9 Grant, R. T., and Viko, L. E. Observations on the Anatomy of the Thebesian Vessels of the Heart, *Heart* **15** 103, 1929.

10 Stella, G. The Part Played by the Thebesian Vessels in the Blood Supply to the Heart, *J. Physiol.* **73** 36, 1931.

# TREATMENT OF ELDERLY DIABETIC PATIENTS WITH CARDIOVASCULAR DISEASE

AVAILABLE CARBOHYDRATE AND THE BLOOD SUGAR LEVEL

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The greater incidence of arteriosclerosis in diabetic patients and the younger age groups in which it occurs have long been recognized. More recently diabetes has come to be regarded as one of the important causes of angina pectoris. With the advent of insulin, the prolongation of diabetic life, especially as regards children, has rendered the problem of this form of cardiovascular disease more pressing.

The etiologic relationship between diabetes and cardiovascular disease and the problem involved in the treatment of these allied conditions have been the subjects of much speculation with but a slow advance in knowledge. The introduction of insulin has not made matters much clearer. On the contrary, the more rigid control of the metabolic disturbance made possible by the use of this hormone has made it evident that during the rigorous treatment of the diabetic symptoms, the cardiovascular status of the patient may not only remain unimproved, but may often be appreciably influenced in an adverse direction. The literature contains many references, both clinical and experimental, to the deleterious effects of insulin shock on the myocardium. The reports vary from the precipitation of decompensation or anginal attacks in diabetic patients with a damaged myocardium, to actual fatalities preceded by such phenomena. More recently electrocardiographic studies have been made with the view of gaining a more intimate knowledge of the effect of insulin hypoglycemia on the heart. The recent paper of Middleton and Oatway<sup>1</sup> (which contains an excellent bibliography of the afore-

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<sup>1</sup> Middleton, W S, and Oatway, W H. Insulin Shock and the Myocardium, *Am J M Sc* **181** 39, 1931

mentioned literature) reports a series of such observations. The chief electrocardiographic variation that they observed was, in confirmation of previous workers, a flattening or inversion of the T wave. Other less constant findings were an increase in the A-V conduction time and a depressed P wave. These observations are also in agreement with the results of electrocardiographic studies by Wittgenstein and Mendel,<sup>2</sup> by von Haynal<sup>3</sup> and by others on the hearts of lower mammals.

There can be no doubt that insulin hypoglycemia represents a definite and characteristic insult to the myocardium. Middleton and Oatway,<sup>1</sup> however, reported similar though less marked results in four cases in which the insulin did not lower the blood sugar below 70 mg per hundred cubic centimeters. These results seem to lend support to the opinions of von Haynal, Vidovszky and Gyorgi<sup>4</sup> and of Schaffer, Bucka and Friedlander,<sup>5</sup> that the electrocardiographic changes are due to a direct action of insulin (or a component) on the heart, rather than to the accompanying hypoglycemia. One of us (J. Soskin<sup>6</sup>) has recently shown that the diabetic organism as a whole suffers little if any impairment in its ability to oxidize carbohydrate. The difficulties involved in the determination of the utilization of carbohydrate by the isolated diabetic heart have led to contrary reports and conclusions.<sup>7</sup> When it is remembered, however, that few if any of the diabetic patients under consideration are completely diabetic, it must be realized that the carbohydrate requirement of their hearts cannot be disregarded. Furthermore, as Middleton and Oatway<sup>1</sup> pointed out, none of their patients had hearts that could be considered normal. In view of the work of Smith, Gibson and Ross<sup>8</sup> and of others on the beneficial effects of high carbohydrate diets in the relief of congestive heart failure, it seems likely that the pathologic heart requires a greater amount of carbohydrate than the normal heart. This may account for the results of

2 Wittgenstein, A., and Mendel, B. Die Veränderung der T-Zacke des Elektrokardiograms während der Insulinwirkung, *Klin Wchnschr* **3** 1119, 1924.

3 von Haynal, E. Elektrokardiographische Untersuchungen über Insulinwirkung auf das Herz II, *Klin Wchnschr* **4** 1729, 1925.

4 von Haynal, E., Vidovszky, L., and Gyorgi, G. Elektrokardiographische Untersuchungen über Insulinwirkung auf das Herz, *Klin Wchnschr* **7** 1543, 1928.

5 Schaffer, H., Bucka, E., and Friedlander, K. Ueber die Einwirkung des Insulin und der Hypoglykämie auf das menschliche Herz, *Ztschr f d ges exper Med* **57** 35, 1927.

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7 Cruickshank, E. W. H., and Shrivastava, D. L. The Action of Insulin on the Storage and Utilization of Sugar by the Isolated Normal and Diabetic Heart, *Am J Physiol* **92** 144, 1930.

8 Smith, F. M., Gibson, R. B., and Ross, N. G. The Diet in the Treatment of Cardiac Failure, *J A M A* **88** 1943 (June 18) 1927.



Middleton and Oatway<sup>1</sup> on insulin without hypoglycemia, since the blood sugars of their patients, although not abnormally low for the normal heart, may represent a state of relative hypoglycemia for the diseased myocardium. A similar explanation may apply to the work of Parsonnet and Hyman,<sup>9</sup> who observed the development of the stenocardial syndrome in diabetic patients with old coronary thrombosis, following doses of insulin that did not produce hypoglycemia.

It was with particular reference to these latter considerations that the work here presented was undertaken. If insulin exerts a direct deleterious action on the myocardium, then its continued administration to diabetic patients with cardiovascular disease, even though never sufficient to produce hypoglycemia in the usual sense, must be viewed with some apprehension. If, on the other hand, the hypoglycemia, whether absolute or relative, is responsible for the cardiac embarrassment, then the diet accompanying the insulin must be of paramount importance. In the following experiments we have attempted to evaluate the influence of insulin and of diet on the cardiovascular status of elderly diabetic patients with cardiovascular disease.

#### METHODS

Seven elderly diabetic patients with clinical evidence of coronary sclerosis or angina pectoris were studied. These patients remained in the Max Pam Metabolism Unit throughout the entire period of each experiment. Six patients were kept for from two to four weeks on accurately controlled diets which permitted their accustomed high blood sugar level and glycosuria, no attempt being made to control the diabetic manifestations to a greater extent than was usual with each patient before entrance to the hospital. This period was followed by a similar period in which the diet remained unchanged but insulin was used in therapeutic doses. During the latter period the blood sugar was kept at a low normal level, but at no time was sufficient insulin given to produce persistent hypoglycemia. One patient with mild diabetes, who was particularly suitable for the purpose, was given no insulin throughout the experiment, her diabetic manifestations being controlled by diet alone. For this patient alternating periods of high and low carbohydrate diet were used.

In addition to the usual clinical observation and the routine daily urinalysis of these patients, quantitative twenty-four hour determinations of the excretion of dextrose and nitrogen in the urine and the fasting blood sugar level were determined daily. The blood cholesterol and the carbon dioxide content of the venous blood were determined twice a week. Observation of the cardiovascular system was limited to daily measurements of the blood pressure and pulse rate and the recording of electrocardiograms twice a week. A great many additional electrocardiograms and related observations were made at various times when the patients manifested unusual symptoms or complained of untoward subjective states. Further experiments, which will include observations on the peripheral vascular system, are projected.

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<sup>9</sup> Parsonnet, A. E., and Hyman, A. S. Insulin Angina, *Ann Int Med* 4: 1247, 1931.

As a basis for comparison with previous studies, each of our patients was subjected to one or more acute experiments. After a control period of observation, a single large dose of insulin was administered. The pulse rate, respiratory rate, arterial blood pressure, blood sugar level and electrocardiogram were determined at frequent intervals before and after the administration of the insulin. After sufficient time had elapsed for the development of a significant hypoglycemia, dextrose was administered intravenously and by mouth, and the observations were continued.

#### RESULTS OF ACUTE EXPERIMENTS

The results obtained in the acute experiments are presented herewith first both because the phenomena observed were of greater magnitude than those obtained in the therapeutic experiments and because they are necessary for the interpretation of the latter. These acute experiments differ from most of those previously reported in that the administration of an overdose of insulin was given after the patients had been observed under controlled conditions over relatively long periods of time. This procedure enabled us to procure several observations while the patient was comfortably at rest before receiving insulin during the development of hypoglycemia after the administration of insulin and during the recovery from hypoglycemia following the administration of sugar.

Typical acute experiments are shown in the summary protocols (figs 1 and 2). For purposes of brevity and clarity, the results in these protocols and others are summarized under the appropriate subheadings.

*Respiration and Blood Pressure*—No significant change in respiratory rate was observed. The blood pressure tended to drop during the course of action of insulin. Thus, the systolic and pulse pressures dropped in five of nine experiments (fig 1), remained practically unchanged in two and rose in two experiments. The rise in blood pressure in one of the latter experiments was associated with an attack of paroxysmal auricular fibrillation (fig 2). The diastolic pressure fell in four of nine experiments (fig 2), remained unchanged in four, and temporarily rose in one (fig 1). After the administration of sugar there was in many cases a tendency for the blood pressure to be restored toward normal. However, the experiments shown in figures 1 and 2 are exceptions and fail to show this restoration. The tendency for the administration of sugar to restore the blood pressure level favors the view that insulin rather than rest in bed during the experiment was chiefly responsible for the previous drop in blood pressure. It was observed that whenever patients became uncomfortable or apprehensive there was a temporary rise in blood pressure. Thus, in many cases, when the symptoms of insulin shock became marked, a rise in blood pressure was seen. A temporary rise in blood pressure often occurred when the insulin or sugar solution was injected (viz., effect of sugar solution in fig 1).

TIME		PULSE RATE	RESPN RATE	ART BLOOD PRESS	BLOOD SUGAR	ELECTROCARDIOGRAMS		
						LEAD I	LEAD II	LEAD III
P M		PER MIN	PER MIN	MM HG	MGMS %			
1 45	PESTING COMFORTABLY	84	18	$\frac{152}{60}$	296			
200 40 UNITS INSULIN INJECTED SUBCUTANEOUSLY								
2 30	NO COMPLAINTS	76	18	$\frac{135}{73}$	204			
3 00	NO COMPLAINTS	86	18	$\frac{138}{78}$	206			
3 40	TRICEMIAL PULSE AT WRIST	88	17	$\frac{125}{60}$	106			
4 30	COMPLAINS OF HUNGER	80	18	$\frac{118}{64}$	44			
4 38-4 43 50 CC OF 50% GLUCOSE INJECTED INTRAVENOUSLY								
4 50	TRICEMIAL PULSE AT WRIST	76	18	$\frac{128}{60}$	190			
5 40	TRICEMIAL PULSE AT WRIST	88	18	$\frac{118}{62}$	72			

Fig 1—Summary protocol of acute experiment on Harry S

Our series offers as much variability in the changes in the blood pressure following the administration of insulin as reported in the literature (Middleton and Oatway<sup>1</sup>), but on the whole our results show that aside from the effects of subjective distress, the blood pressure—systolic, diastolic and pulse—tends to fall during insulin hypoglycemia.

*Heart Rate and Rhythm*—The changes in heart rate, like the changes in blood pressure, were variable. Similar variability was reported in the literature (Middleton and Oatway<sup>1</sup>). In three experiments the rate fell during the insulin effect, in five experiments the rate increased (in two of the latter the change occurred only during insulin shock), while in one experiment the rate remained unchanged (fig 1). It is interesting to note that in the case shown in figure 2 there was an increase in rate before the cardiac mechanism changed. The administration of sugar did not always restore the rate to normal. Just as in the case of the blood pressure, the changes in heart rate are complicated by the effects of psychic distress.

Several changes in the mechanism of the heart were observed. A striking sinus arrhythmia developed in one patient at the point of maximum hypoglycemia. The slowing of the heart rate and sinus arrhythmia may be due to a direct action on the sinus node or to an influence on the vagus nerves, either centrally or peripherally. The inconstancy of the results indicates that other mechanisms, such as reflex acceleration following lowering of the blood pressure, may also operate.

Insulin apparently increases the irritability of ectopic foci. Extrasystoles developed in three cases, the origins being auricular, ventricular (fig 2, 1-40) and nodal, respectively. In a second experiment on the patient in figure 1, the extrasystoles that were present at the start were increased in frequency during the insulin period. The administration of sugar caused a disappearance of the ectopic rhythm, except in the last mentioned experiment, in which their frequency was reduced. Similar changes have been reported by others, especially Schaffer, Bucka and Friedlander,<sup>5</sup> who also noted the occurrence of auricular fibrillation. A striking instance of paroxysmal auricular fibrillation accompanied by a typical attack of angina pectoris was found in the patient whose protocol is shown in figure 2. This mechanism was temporarily converted to a sinus tachycardia after the administration of sugar intravenously (fig 2, 2-45), coincident with the relief of the angina pectoris. This last change could not have been diagnosed without the electrocardiogram, because the irregular pulse deficit at the wrist persisted. Auricular fibrillation, however, soon returned without the angina and lasted until the next morning.

*Symptomatic Changes*—In addition to the occurrence of some or all of the typical symptoms of insulin shock, typical attacks of angina

TIME		PULSE RATE	RESPN RATE	ART BLOOD PRESS	BLOOD SUGAR	ELECTROCARDIOGRAMS		
						LEAD I	LEAD II	LEAD III
P M 12 40	RESTING COMFORTABLY	PER MIN 72	PER MIN 24	MM HG $\frac{184}{106}$	MGMS % 56			
12 50 25 UNITS INSULIN INJECTED SUBCUTANEOUSLY								
1 10		112	24	$\frac{180}{100}$	52			
1 30	COMPLAINS OF THIRST	112	24	$\frac{212}{90}$	68			
1 40	AURICULAR FIBRILLATION AUSCULTATED 135 COMPLAINS OF PRECORDIAL PAIN	96	24	$\frac{212}{80}$	36			
2 10	PRECORDIAL PAIN RADIATING TO LEFT ARM INCREASING THIRST	115- 125	26	$\frac{200}{90}$	27			
2 15-2 20 3 OUNCES ORANGE JUICE + 3 TEASPOONFUL CANE SUGAR TAKEN BY MOUTH								
2 25-2 40 50 CC OF 50% GLUCOSE INJECTED INTRAVENOUSLY								
2 45	COMPLAINS OF EXTREME FATIGUE NO PAIN	99	26	$\frac{200}{90}$	107			
3 00	FEELS MUCH BETTER DESIRES TO URINATE	103	26	$\frac{206}{90}$	110			
4 40	SLEPT FOR FEW MINUTES RESTING COMFORTABLY	104	24	$\frac{212}{100}$	82			

Fig 2—Summary protocol of acute experiment on Lena S

pectoris developed in two cases. All of these symptoms were relieved after the administration of dextrose.

*Electrocardiographic Changes*—P wave and P-R interval. The changes in the P wave were variable. In all but three experiments on two patients it became shorter and more peaked. In the others, it became longer and more notched (fig 1). The P-R interval remained unchanged in many of the experiments. In one it lengthened slightly (fig 1), in three, in which the P wave became shorter, it also became shorter.

QRS complex. In all experiments the QRS complex became smaller in one or more leads. In two experiments the QRS complex became more slurred. In two experiments on one patient, in which the QRS complex was at the upper limits of normal, the duration became slightly longer after the administration of insulin (fig 1). There was a tendency for restitution with the administration of sugar. No axis shift was noticed. These changes in the QRS complex and in the P wave and P-R interval are in accord with the results of previous workers (Middleton and Oatway<sup>1</sup>).

S-T segment and T wave. Much more striking and consistent findings were observed in these portions of the electrocardiogram following the administration of insulin. The changes in the S-T segment and T wave were found to depend on the direction of the major deflection of the QRS complex, a correlation hitherto overlooked. Thus, in lead I, in which the major initial complex was upright, the S-T segment became negative (fig 3). When the QRS complex was negative to begin with, the deviation of the S-T segment from the iso-electric level increased, and it changed from a horizontal to a descending line (figs 1 and 2). In the few cases in which the major initial deflection was upright in lead III, the S-T segment in that lead became negative. In most cases, however, the major deflection of the QRS complex was inverted in lead III, and the S-T segment in this lead became positive (fig 3) or its deviation above the iso-electric line increased, and at the same time it tended to change from a horizontal to an ascending line (figs 1 and 2). While the changes in the S-T segment in lead II fell into the same category, they were less striking, and exceptions occurred in two cases in which the amplitude of the QRS complex was small. Thus, in figures 1 and 2 the changes were as anticipated, while in figure 3 there was no shift in the S-T segment.

The T wave in lead I, which in our series was upright in all cases to start with, became flatter, lost its peaklike quality and increased in duration after the administration of insulin (figs 2 and 3). In two instances it became diphasic (fig 1), and in one case it became indiscernible. The T wave in lead III started out as a cove-shaped negative wave in the majority of our cases, associated in every instance with an inverted major deflection (figs 1, 2 and 3). With insulin, the T wave

became less negative, its duration increased, its cove-shaped appearance disappeared, and in some cases it became indiscernible or even upright (figs 1, 2 and 3). In one experiment, a positive T wave in lead III, associated with an inverted major initial deflection, became larger during the effect of insulin. In two other experiments on another subject the upright T wave in lead III, associated with an upright major initial deflection, became longer and flatter after the administration of insulin.

The changes in lead II were of a similar nature (fig 1). However, in two instances (figs 2 and 3) the changes in the T wave were not in line with the other experiments, thus, in one case (fig 2) a negative T

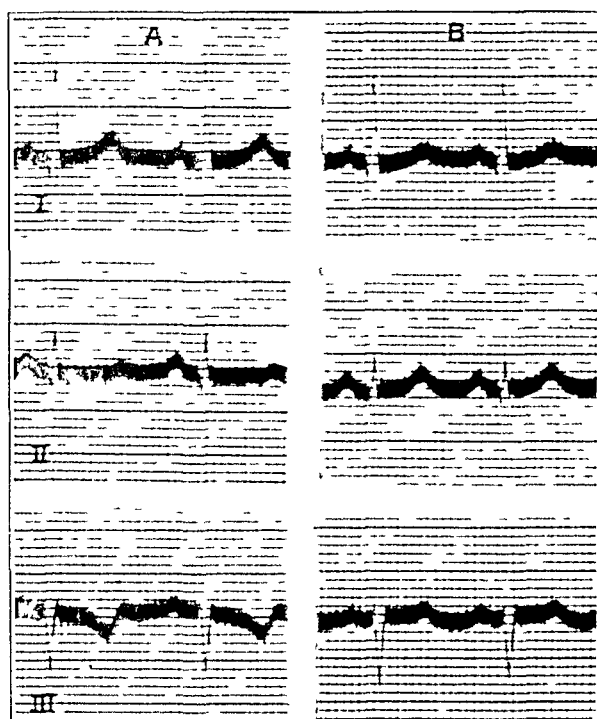


Fig 3—Electrocardiograms (three leads), showing effect of insulin on Aaron L. A was taken as a control before insulin was given, B, after the administration of insulin. Note the reversal of direction from an inverted to an upright T wave in lead III.

wave in lead II, with an upright major initial deflection, became positive, and in the other (fig 3), an upright T wave in lead II, with an upright major initial complex, became larger. The variability of lead II as regards both the T wave and the S-T segment, is apparently due to the manner in which the effects in leads I and III summate; it is comparable to the normal variability of these parts of the electrocardiogram in lead III. It follows that in studies similar to this lead I and lead III are of more significance than lead II.

All of the foregoing electrocardiographic changes tended to be restored to the preinsulin status after the administration of dextrose.

## RESULTS OF THERAPEUTIC EXPERIMENTS

The details of the therapeutic experiments, except for the electrocardiographic data, are summarized in table 1. Because of limitation of space, the figures presented are averages for the periods indicated. Actual figures for typical days are given in the summary protocols,

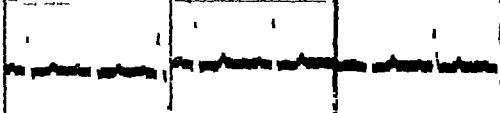
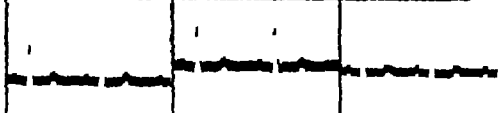
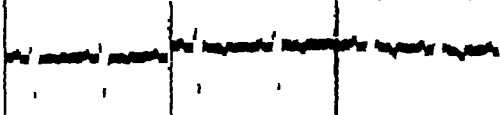
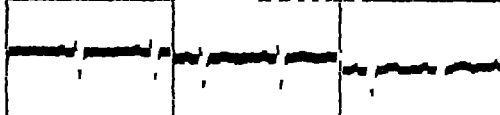
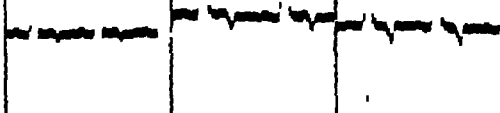
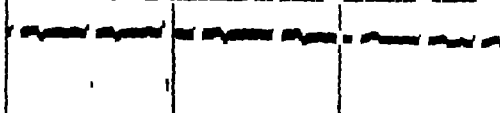
DAY OF EXPT		2ND	8TH	13TH	INSULIN STARTED ON 19TH DAY	27TH	38TH	40TH	
DIET	CHO	GMS 75	75	75		75	75	75	
	FAT	GMS 100	100	100		100	100	100	
	PROT	GMS 50	50	50		50	50	50	
	CALS	1400	1400	1400		1400	1400	1400	
AVAILABLE CHO		GMS 114	114	114		114	114	114	
INSULIN		UNITS 0	0	0		42	46	30	
FASTING BLOOD SUGAR		MGMS % 229	170	250		61	53	133	
GLYCOSURIA-24 HR		GMS 10.2	15.6	15.7		0.48	0.36	2.61	
NITROGEN EXCRETION-24 HR		GMS 5.97	7.81	7.40		7.33	7.33	4.77	
CO <sub>2</sub> CONTENT VENOUS BLOOD		VOLS % 57.1	57.8	56.1		52.7	55.5	52.3	
ARTERIAL BLOOD PRESSURE		MM HG $\frac{150}{80}$	$\frac{146}{80}$	$\frac{148}{78}$		$\frac{154}{80}$	$\frac{150}{80}$	$\frac{146}{78}$	
PULSE RATE		PER MIN 84	74	90		88	76	78	
ELECTROCARDIOGRAMS	LEAD I								
	LEAD II								
	LEAD III								

Fig. 4—Summary protocol of typical days during two periods of therapeutic experiment on Harry S.

figs. 4 and 5. The time periods given in table 1 represent periods of consecutive days considered suitable for comparison with other periods. They do not include intermediate periods of adjustment and therefore do not indicate the total length of time necessary for each study.

Great care was taken to keep the intake of food constant throughout the experimental periods. The caloric value of the diets was set at a



low level in order to avoid a masking of their effects by the sheer abundance of energy material. It will be seen, however, that only two of the patients (Esther B and Ottile P), who were overweight to begin with, lost any appreciable amount of weight while on experiment. The types of diet used for the various patients varied from moderately low to moderately high carbohydrate mixtures. One patient (Ben S) differed from the rest in that he received insulin during both experimental periods, the contrast in his case being made between a relatively low and a relatively high administration of insulin while on a constant diet. Another patient (Esther B) was observed during two cycles, with and without insulin, the diet of one complete cycle being different from that during the other. The last patient (Lena S) received no insulin whatever throughout her therapeutic experiments, the diet alone being varied from a low to a high carbohydrate mixture.

The chemical data in table 1 show the average extent to which the fasting blood sugar level and the glycosuria varied during the different experimental periods. It may be seen that the fasting blood sugar values did not fall below those ordinarily considered normal and that some glycosuria usually persisted even during the insulin periods. The figures for the excretion of urinary nitrogen indicate the protein-sparing action during the insulin periods. This was probably due to the retention, during these periods, of dextrose which appeared in the urine in the absence of insulin.

The changes in blood pressure and heart rate which occurred during the insulin periods were slight and inconstant. It is interesting to note that those patients who did show some rise in blood pressure both systolic and diastolic, during the administration of insulin were receiving the higher carbohydrate diets. In these patients also, the pulse rate tended to increase. The patients on the lower carbohydrate mixtures showed little or no change in blood pressure and a decrease in pulse rate during the insulin periods. The patient (Lena S) who did not receive insulin showed a higher blood pressure and a lower pulse rate during the high carbohydrate periods than during the low carbohydrate periods. The effect of insulin on the cardiac rhythm was more definite. It usually increased the incidence of ectopic beats, and in one case (fig 4) it produced a series of auricular extrasystoles leading to pulsus trigeminus.

The electrocardiographic changes during the insulin periods were similar to, though of lesser magnitude than those caused by insulin in the acute experiments (compare figs 1 and 4). The records obtained during the different periods of the therapeutic experiments were measured for the duration and amplitude of the various phases of the

electrocardiogram These data were checked by an inspection of the curves to estimate the changes in contour that the measurements failed to reveal

A comparison of the insulin periods with those periods in which insulin was omitted showed, without exception, one or more of the

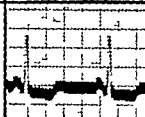
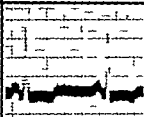
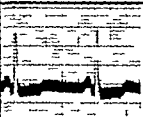
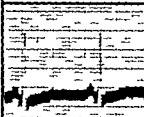
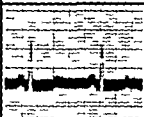
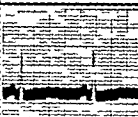
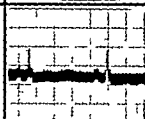
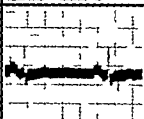
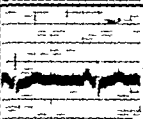
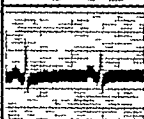
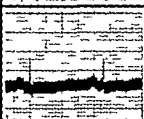
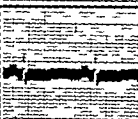
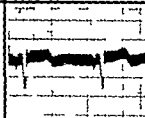
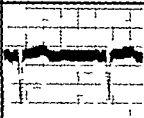
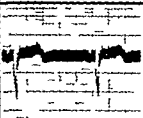
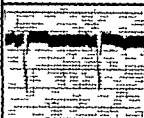
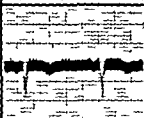
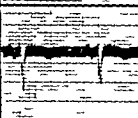
DAY OF EXPT		3RD	13TH	31ST	DIET CHANGED ON 32ND DAY	34TH	45TH	52ND
DIET	CHO	GMS 50	50	50		160	160	175
	FAT	GMS 100	100	100		50	50	55
	PROT	GMS 50	50	50		50	50	50
	CALS	1300	1300	1300		1290	1290	1395
AVAILABLE CHO		GMS 89	89	89		194	194	209.5
INSULIN		UNITS 0	0	0		0	0	0
FASTING BLOOD SUGAR		MGMS % 60	63	93		90	101	75
GLYCOSURIA-24 HR		GMS 0.49	0.42	0.34		0.44	0.62	0.37
NITROGEN EXCRETION-24 HR		GMS 5.18	4.90	7.51		3.18	4.74	5.22
CO <sub>2</sub> CONTENT VENOUS BLOOD		VOL. % 55.1	50.4	58.1		49.7	48.5	59.4
ARTERIAL BLOOD PRESSURE		MM HG $\frac{140}{70}$	$\frac{150}{70}$	$\frac{183}{100}$		$\frac{187}{100}$	$\frac{190}{95}$	$\frac{190}{86}$
PULSE RATE		PER MIN 80	78	74		66	72	72
ELECTROCARDIOGRAMS	LEAD I							
	LEAD II							
	LEAD III							

Fig 5—Summary protocol of typical days, when sinus rhythm was present, during two periods of therapeutic experiment on Lena S

following changes during the former period (a) a slight prolongation of the P-R interval, (b) a slight prolongation of the QRS complex, (c) a diminution of the amplitude of the QRS complex in all leads to varying extents, (d) a tendency for the S-T interval to shift slightly in the direction opposite to the major initial complex, (e) an increase in duration of the T wave, (f) an increase in the height of the T wave when it was originally opposite in direction to the major initial complex

and a decrease in the height of the T wave when it was originally in the same direction as the major initial complex, in several patients (fig 4) the T wave changed its direction, (g) a variable change in amplitude, duration and, sometimes, direction in the P wave

While these changes are not as striking as those observed in the acute experiments, taken by and large, they are in accord with the changes described in the acute experiments and noted by previous observers. The magnitude of the electrocardiographic deviations induced by insulin did not depend on the absolute level at which the blood sugar was maintained (table 1). Analysis of individual protocols indicated that the length of time over which insulin was administered and the extent of the change from the accustomed blood sugar level to the new level were important factors.

The subjective reactions of our patients to the experimental procedure were in surprising accord with our objective findings. They invariably complained of a decreased sense of well-being during the periods of administration of insulin. The usual complaints were weakness and prostration, dizziness, nervousness, palpitations, precordial pain and constriction, which in some cases (Ottile P., Esther B. and Lena S.) amounted to typical attacks of angina pectoris. Harris I. refused to continue on insulin because he "felt bad all the time."

The therapeutic experiments (Esther B. and Lena S.) in which a comparison of low and high carbohydrate diets was made were particularly informative. The results were similar in both cases. The case of Lena S., who received no insulin except for her acute experiment, deserves special mention. This patient had been treated for her diabetes with a low carbohydrate diet for many months prior to her admission to the Max Pam Unit. A similar initial diet was therefore prescribed for our study (table 1). At this time the patient complained of weakness, evidenced a moderate degree of cardiac decompensation and suffered from attacks of angina pectoris accompanied by paroxysmal auricular fibrillation (fig 6) from three to four times a week. The substitution of a high carbohydrate diet for the low one produced a startling result. She did not have a single attack of angina pectoris or auricular fibrillation while on the high carbohydrate diet, and her clinical state improved to the extent that we found it difficult to keep her at constant rest in bed. These results were confirmed by repetition. Indeed, her subjective reaction to the second period of low carbohydrate diet was so severe that it had to be cut short. The return to the high carbohydrate diet was again followed by remarkable improvement, her only attack during this period being precipitated when she walked down a long hospital corridor and up several stairs in order to use a telephone.

TABLE 1—Summary of Therapeutic Experiments

Patient	Comment	Period	Diet				Duration, Days	Insulin, Average Daily Units	Fasting Blood Sugar, * Mg per 100 Cc	Average Urinary Glucose, Gm per 24 Hrs	Average Morning Blood Pressure, mm Hg	Average Morning Pulse Rate, per Min	Subjective Complaints
			Calories	Protein	Fat	Carbohydrate							
Harry S	Aged 63, a white man, weight on admission, 15 Kg, on discharge, 15 Kg	Control					18						
	Diagnosis Diabetes mellitus, arteriosclerotic heart disease	Insulin	1,400	50	100	75	23	0	225	13.5	7.9	110/79	91
Laron L	Aged 44, a white man, weight on admission, 64 Kg, on discharge, 63 Kg	Control	1,400	50	100	75	11	0	80	1.6	7.5	139/78	83
	Diagnosis Diabetes mellitus, arteriosclerotic heart disease advanced peripheral arteriosclerosis	Insulin	1,525	50	125	50	23	0	118	1.0	8.1	155/81	95
Ottilie P	Aged 61, a white woman, weight on admission, 79 Kg, on discharge, 74 Kg	Control	1,525	50	125	50	1	24	70	0.5	6.9	155/81	81
	Diagnosis Diabetes mellitus, arteriosclerotic heart disease, mild congestive heart failure, obesity	Insulin	1,475	40	75	150	21	0	152	6.5	6.9	153/75	68
Harris I	Aged 64, a white man, weight on admission, 44 Kg, on discharge, 44 Kg	Control	1,475	40	75	150	18	28	111	2.0	6.6	137/77	71
	Diagnosis Diabetes mellitus, arteriosclerotic heart disease	Insulin	1,485	65	85	140	9	0	166	11.6	10.4	109/68	7
Ben S	Aged 68, a white man, weight on admission, 44 Kg, on discharge, 50 Kg	Insulin	1,485	65	85	140	8	70	85	0.8	8.4	119/76	80
	Diagnosis Diabetes mellitus, arteriosclerotic heart disease, mild congestive heart failure	More insulin	1,520	50	120	60	25	19	277	38.0	8.7	135/76	80
Isther B	Aged 55, a white woman, weight on admission, 107 Kg, on discharge, 100 Kg	Control	1,520	50	120	120	15	38	115	3.7	6.0	134/73	71
	Diagnosis Diabetes mellitus, rheumatic heart disease, mild congestive heart failure, angina pectoris, obesity	Insulin	1,360	60	80	80	19	0	193	4.3	12.8	104/71	72
Lena S	Aged 55, a white woman, on admission, could not be weighed, on discharge, 56 Kg	Control	1,360	60	80	80	11	50	109	3.0	14.8	111/76	72
	Diagnosis Diabetes mellitus, arteriosclerotic heart disease, moderate congestive heart failure, angina pectoris with paroxysmal gitter	Insulin	1,040	50	80	75	13	0	162	4.3	13.0	100/65	71
		Low carbohydrate	1,040	50	100	50	31	55	87	3.2	9.9	109/75	70
		High carbohydrate	1,300	0	50	100	32	0	74	0.5	5.5	165/82	75
		Low carbohydrate	1,200	50	50	100	160	0	85	0.5	5.0	188/94	72
		High carbohydrate	1,300	50	50	100	8	0	87	0.7	4.6	196/99	72
		High carbohydrate	1,540	50	60	200	36	0	107	1.4	4.5	202/100	69
		High carbohydrate											

\* "True" blood sugar values were determined by the Somogyi modification of the Shaffer-Hartmann method, which yields results approximately 20 mg. per hundred cubic centimeters lower than in the Folin Wu method.

† This patient's diabetes was mild, but the following results were obtained in a typical carbohydrate tolerance test: fasting blood sugar level, 86 mg., 100 Gm. of dextrose by mouth, one half, one hour and two hours later, the blood sugar levels were 221, 252, and 366 mg. per hundred cubic centimeters, respectively.

The summary protocol in figure 5 shows three typical days from each of the first two experimental periods on this patient. The changes in the electrocardiogram are the same as those already described in the acute and therapeutic experiments with insulin. The depression of the S-T segment in leads I and II and its elevation in lead III during the low carbohydrate diet are striking, as is also the conversion of the negative T wave of lead III to an upright one. The QRS complex in this patient, unlike that in the others, became larger while the patient was on a low carbohydrate diet, a change also noted in her acute experiment with insulin. It is interesting to note that the blood pressure

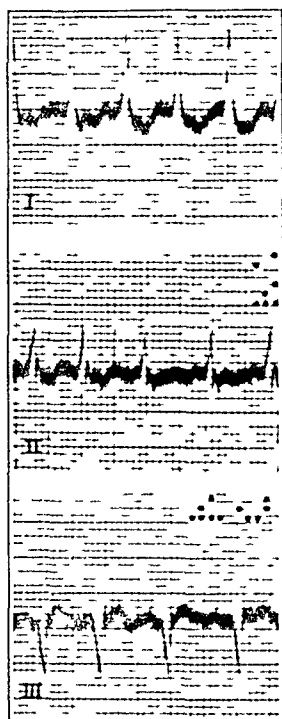


Fig 6—Electrocardiogram taken during an attack of paroxysmal auricular fibrillation accompanied by angina pectoris, which appeared during the low carbohydrate period in Lena S.

during the time the patient was on a low carbohydrate diet was lower than that during the time she was on a high carbohydrate diet, and that the pulse rate was faster in the former period. These changes were consistent and may have been associated with the angina and paroxysms of auricular fibrillation. A similar change in blood pressure was also observed in Esther B.

The results with these two patients show that low carbohydrate diets produce the same effects on the heart as are produced by the therapeutic use of insulin. This effect of the low carbohydrate diet is associated with a relatively small change in the blood sugar level. But the greater

amount of carbohydrate readily available to the damaged myocardium in the high carbohydrate diet would seem to be the significant factor for the well-being of these patients. This is in accord with the recent studies of Smith and his associates<sup>8</sup> on the beneficial effect of high carbohydrate diets on patients with heart failure.

#### COMMENT

Our results confirm the work of previous investigators in regard to the characteristic manifestations of cardiac impairment caused by insulin hypoglycemia. They further indicate that similar manifestations may be produced in elderly diabetic patients by the therapeutic administration of insulin over longer periods of time. The cardiovascular phenomena accompanying the therapeutic use of insulin are of lesser magnitude than those caused by insulin shock, but they occur at blood sugar levels within the usually accepted normal range. The objective phenomena resulting from insulin therapy, like those caused by insulin hypoglycemia, are accompanied by subjective distress. In both cases the signs and symptoms are abated with the return of higher blood sugar levels.

The electrocardiographic changes following the administration of insulin led us to believe that the heart suffers a depression, which affects conduction in particular. This agrees with the conclusion of Schaffer, Bucka and Friedlander,<sup>9</sup> and is in accord with the well known fact that of all the cardiac properties, conductivity is the most labile. Our conclusions are based on the finding of a decreased amplitude and an increased slurring of the QRS complex, and are further supported by the tendency of the S-T segment and the T wave to shift in a direction opposite to the major initial complex. This is so striking in certain cases as to resemble the changes seen during attacks of angina pectoris, such as reported by Feil and Siegel.<sup>10</sup> In fact, in one of our cases (fig. 2) these changes preceded the attack of angina pectoris.

One of us (L. N. K.<sup>11</sup>), in reviewing the significance of the T wave, has pointed out that the direction of the T wave is determined by two factors: (a) the asynchronism of the onset of activity in various fractions of the heart, which, if acting alone, would tend to make the T wave a mirror image of the QRS complex so far as direction is concerned, and (b) the unequal duration of activity of the various fractions of the heart. It is the latter factor that is responsible for the T wave being normally in the same direction as the major initial complex. It follows,

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10 Feil, H. S., and Siegel, M. L. Electrocardiographic Changes During Attacks of Angina Pectoris, *Am J M Sc* **175** 255, 1928.

11 Katz, L. N. The Significance of the T Wave in the Electrogram and Electrocardiogram, *Physiol Rev* **8** 447, 1928.

therefore, that any tendency for the T wave to become opposite in direction to the major initial complex can mean (a) that the inequality in the duration of activity in the various heart fractions is decreased, (b) that the asynchronism of the onset of activity is increased, i. e., conduction is slowed, or (c) that both factors operate. In view of the other changes noted in the electrocardiogram, it is more logical to explain the changes on the basis of a delay in conduction. The previous reports that insulin causes inversion of the T wave were probably made because the authors were dealing with upright major initial deflections.

The analysis of the changes in the S-T segment is complicated because there are two possible causes for the shifts in this segment: (a) the injury of large regions of the heart, usually due to myocardial ischemia, and (b) the beginning of the recovery process in this segment, so that a sharp differentiation between the S-T and the T wave is not always feasible. The fact that during the period that insulin is being administered the S-T segment slopes to meet and fuse with the T wave favors the view that the explanation proposed for the change in the T wave holds, in part at least, for the S-T segments. If, as Ernstene and Altschule<sup>12</sup> have concluded, insulin causes an increase in the minute volume of circulation and this applies equally to the heart with coronary sclerosis, it is not unlikely that the coronary supply will fail to keep pace with the work of the heart. Myocardial ischemia, with its electrocardiographic and anginal signs, would therefore follow (Katz and Wallace<sup>13</sup> and Feil and Siegel<sup>10</sup>).

The case (Lena S.) in which the deleterious effects of insulin on the heart were reproduced by the use of a low carbohydrate diet alone is of particular significance in elucidating the mechanism by which insulin produces its effects. The fact that no insulin was administered throughout this therapeutic experiment rules out the possibility of ascribing our results to the presence of a toxic component in commercial insulin. An excess of endogenous insulin can hardly be postulated since the patient had diabetes. The experimental impairment of the myocardium in this patient cannot, therefore, be due to either an excess of insulin in the organism or a toxic component of administered commercial insulin. The effects observed must therefore be ascribed to the lack of readily available carbohydrate for the use of the already damaged heart. The relief of the objective manifestations and subjective symptoms of her cardiac distress by the high carbohydrate diet was striking. The hypoglycemic rather than the direct toxic action of insulin is also

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12 Ernstene, A. C., and Altschule, M. D. The Effect of Insulin Hypoglycemia on the Circulation, *J. Clin. Investigation* **10** 521, 1931.

13 Katz, L. N., and Wallace, A. W. The Role of Cardiac Ischemia in Producing R-T Deviations in the Electrocardiogram, *Am. J. M. Sc.* **181** 836, 1931.

indicated by the case (Ben S) in which the patient received insulin during both experimental periods, but in whom the characteristic phenomena developed only when the insulin was sufficient to cause a considerable reduction in his blood sugar level and glycosuria

In most of the experiments with insulin the electrocardiographic changes tended to follow the fluctuations in blood sugar. They did not, however, occur at particular blood sugar levels, nor did the extent of the electrocardiographic variations bear any apparent quantitative relation to the total fall in blood sugar. The rapidity of change in the blood sugar level seemed to be an important factor. The lack of quantitative correlation between the different experiments probably depends on the fact that we were dealing with patients whose hearts were damaged in varying degrees. Our results, like those of Smith and his co-workers,<sup>8</sup> show the increased demands of the impaired myocardium for carbohydrate. It is a most interesting observation that the fact that these patients were diabetic—and this applies especially to the patient who received no insulin—did not prevent the increased requirement of the heart for sugar, or the beneficial action of the increased carbohydrate when given.

The deleterious effect of insulin on the myocardium and the antagonistic action of carbohydrate in this regard seem rather surprising in the light of the generally accepted view that insulin facilitates the utilization of dextrose. This situation is not, however, as paradoxical as it appears at first glance. The function of insulin for which there is most experimental proof is its ability to cause the storage of carbohydrate in the tissues of the organism. If it may be supposed (and we have reason to believe that it is so) that the damaged myocardium stores dextrose only with difficulty, then the lowering of the blood sugar by insulin will decrease or remove the heart's source of dextrose supply without at the same time stocking up the myocardium with its carbohydrate needs for the interim. This would be comparable to a rapid lowering of the blood sugar level in a normal animal. The antagonistic actions of insulin and dextrose on the heart are probably, therefore, more apparent than real.

The clinical aspects of our results have been discussed elsewhere (Strouse, Soskin, Katz and Rubinfeld<sup>14</sup>). We do not think that they should be interpreted to mean that insulin in itself is harmful to the elderly diabetic patient with cardiovascular disease. Our work, however, does indicate that whether or not such patients are receiving insulin, the carbohydrate supply to the damaged myocardium is of the greatest importance.

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14 Strouse S, Soskin S, Katz L N, and Rubinfeld S H. The Treatment of the Older Diabetic with Cardiovascular Disease, *J A M A* **98** 1703 (May 14) 1932



## APPENDIX

The following tables give a description of the electrocardiograms shown in the summary protocols in figures 1, 2, 4 and 5

TABLE 2—*Acute Experiment on Harry S (fig 1)*

	Before Insulin	After Insulin	After Dextrose
QRS complex	Lead I, upright Leads II and III, inverted Slurred in all leads duration, 0.12 second	Smaller amplitude in all leads duration slightly longer	No increase in amplitude, duration decreased
S T interval	Lead I, negative Lead II, iso electric Lead III slightly positive, rising	Lead I, more negative Lead II, slightly negative and rising Lead III, more positive	Lead I, unchanged Lead II, more nearly iso electric Lead III, returns to original configuration
T wave	Lead I, upright Lead II, inverted and small Lead III, inverted and cove shaped	Lead I, progressively smaller Lead II, becomes upright Lead III, progressively smaller, then becomes upright and progressively larger	Lead I, unchanged Lead II, becomes smaller Lead III, becomes smaller
P wave	Upright in all leads small in lead III	Slightly broader	No change
P R interval	0.16 second	0.18 second	0.15 second
Rhythm	Nodal extrasystoles	Extrasystoles increased in frequency	Frequency of extrasystoles decreased

TABLE 3—*Acute Experiment on Lena S (fig 2)*

	Before Insulin	After Insulin	After Dextrose
QRS complex	Lead I, upright Lead II, upright and small Lead III, inverted Slurred in all leads	Lead I, larger Lead II, unchanged Lead III, larger	Lead I, temporarily smaller Lead II unchanged Lead III, temporarily smaller
S T interval	Lead I, negative Lead II, almost iso electric Lead III, positive	Lead I, more negative Lead II, becomes negative Lead III, more positive	Lead I, temporarily iso electric Lead II, temporarily positive Lead III, no change
T wave	Lead I, tiny, upright Lead II, small, inverted Lead III, small, inverted	Lead I, slightly larger Lead II, becomes slightly upright Lead III, becomes almost iso electric	Lead I, temporarily indiscernible Lead II, temporarily larger Lead III, temporarily larger
P wave	Lead I, upright Lead II, small and notched Lead III, inverted	Lead I, taller Lead II, broader and taller Lead III, upright and notched	Lead I, smaller Lead II, narrower Lead III, narrower
P R interval	0.16 second	0.16 second	0.14 second
Rhythm	Sinus rhythm	Paroxysmal auricular fibrillation, ventricular extrasystoles	Temporary sinus tachycardia and later return of auricular fibrillation, extrasystoles disappear

TABLE 4—*Therapeutic Experiment on Harry S (fig 4)*

	Before Insulin	During Insulin
QRS complex	Lead I, upright Leads II and III, inverted Slurred in all leads, duration, 0.12 second	Smaller amplitude in all leads, duration unchanged
S-T interval	Lead I, negative Lead II, iso electric Lead III, positive	Lead I, slightly less negative Lead II, iso electric Lead III, progressively more positive
T wave	Lead I, upright Lead II, inverted and small Lead III, inverted and cove shaped	Lead I, progressively smaller Lead II, becomes iso electric, then progressively more positive Lead III, becomes less negative, then diphasic, then upright
P wave	Upright in all leads	Remains unchanged
P-R interval	0.16 second	Remains unchanged
Rhythm	Slight sinus arrhythmia	Sinus arrhythmia more marked, auricular extrasystoles appear

TABLE 5—*Therapeutic Experiment on Lena S (fig 5)*

	Low Carbohydrate Diet	High Carbohydrate Diet
QRS complex	Lead I, upright Lead II, upright and small Lead III, inverted Slurred in all leads	Lead I, progressively smaller Lead II, slightly smaller Lead III, progressively smaller
S-T interval	Lead I, negative Lead II, slightly negative, rising Lead III, positive, rising	Lead I, less negative Lead II, becomes iso electric Lead III, less positive
T wave	Lead I, small and positive Lead II, small, progressively more positive Lead III, diphasic	Lead I, no change Lead II, becomes negative and small Lead III, becomes negative
P wave	Lead I, upright Lead II, upright Lead III, diphasic	Lead I, smaller, narrower Lead II, smaller, narrower Lead III, no change
P-R interval	0.16 second	0.16 second
Rhythm	Frequent attacks of paroxysmal auricular fibrillation	No attacks of fibrillation

## SUMMARY

1 The characteristic myocardial impairment resulting from insulin hypoglycemia reported by other workers has been confirmed

2 Our results indicate that the changes in the S-T segment and T wave of the electrocardiogram following the administration of insulin depend on the direction of the major deflection of the QRS complex, a correlation hitherto overlooked

3 Similar results have been obtained by the therapeutic use of insulin, in amounts that did not cause hypoglycemia, in the treatment of elderly diabetic patients with cardiovascular disease

4 The results obtained with insulin have also been obtained by the use of a low carbohydrate diet without insulin

5 The objective manifestations of myocardial impairment obtained with both insulin and a low carbohydrate diet were almost always accompanied by complaints of subjective distress in our patients

6 The deleterious action of insulin on the heart is probably not due to a direct toxic action on the myocardium, but is probably related to the supply of carbohydrate that is readily available to this organ

Dr David C Cohn, in the Department of Chemistry, made the chemical analyses

# YELLOW ATROPHY OF THE LIVER

REPORT OF A CASE, WITH PARTICULAR REFERENCE TO THE  
METABOLISM OF COPPER

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AND

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The wide distribution of copper in living materials has been recognized for some time. Elvehjem and Lindow<sup>1</sup> reviewed the older literature with respect to the copper content of plants. The data suggest that copper should be placed in the group of catalytic elements, it is found in greater amounts in more active portions of plants (young shoots, leaves), buds contain more than wood or bark, and its addition to raw peat soil was found to stimulate plant growth. Rose and Bodansky<sup>2</sup> reviewed the older literature with respect to the copper content of animal tissue. With improvement of methods for the detection and quantitative estimation of minute amounts of copper, there is much to support the view that this element is a universal constituent of protoplasm, spectroscopic<sup>3</sup> and chemical<sup>4</sup> analyses indicate its presence in every organ, human and animal. Failure to find it in the past appears to have been due to the limitations of the methods available for its detection when present in minute quantities. Thus, though Palet<sup>5</sup> was unable to find copper in 54 normal human livers, spectroscopic analysis<sup>3</sup> indicates in general, a higher concentration in this organ than in any other organ in the body. The amounts found vary widely. In 160 samples of common food materials, animal and vegetable, the copper content ranged from 0.1 to 44.1 Gm per kilogram of fresh material.<sup>4b</sup>

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1 Elvehjem, C A, and Lindow, C W. J Biol Chem **81** 435, 1929

2 Rose, W C, and Bodansky, M. J Biol Chem **44** 99, 1920

3 Sheldon, J H, and Ramage, H. Biochem J **25** 1608, 1931

4 (a) White, C P. Lancet **2** 701 (Oct 1) 1921. (b) Lindow, C W, Elvehjem, C A, and Peterson, W H. J Biol Chem **81**:435, 1929, **82** 465, 1929. (c) McHargue, J S. Am J Physiol **72** 583, 1925. (d) Maquenne, L, and Demousse, E. Comp rend Acad d sc **170** 87, 1920. (e) Fox, H M, and Ramage, H. Proc Roy Soc, London, s B, **108** 157 (April 20) 1931

5 Palet, L P J, quoted by Bodansky, M. J Biol Chem **48** 361, 1921

## BIOLOGIC SIGNIFICANCE OF COPPER

In the past it was generally held that the presence of copper in biologic materials was of no physiologic significance. In marine life, it was generally attributed to contamination by sea water, and in man, as late as 1925, it was attributed by Malloy<sup>6</sup> to contamination by food. Malloy concluded that "The reason that copper is so generally found in minute quantities in human organs is not due to its being a normal constituent of the tissues but because man is constantly exposed to taking the metal into his system through foods and drinks contaminated with it." The use of copper as a coloring agent for canned foods, its use as a preventative of growth of algae in water and its use in the manufacture of utensils for distillation of liquors were cited as some of the causes of contamination.<sup>7</sup> Malloy, apparently overlooked the extensive work of Rose and Bodansky.<sup>2</sup> From the work of Rose and Bodansky, it would appear that copper is an essential constituent of normal tissue and not an accidental finding due to the ingestion of foods contaminated with this element. There is much to support this view. The wide distribution of copper-containing proteins,<sup>8</sup> the importance of copper in the formation of hemocyanine (Fredericq, 1878) and the relationship between hemocyanine and hemoglobin (Henze, 1901), the rôle of copper in the synthesis of hemoglobin in mammals,<sup>9</sup> its presence in fetal organs in greater concentration than in the corresponding organs of the adult,<sup>10</sup> its presence in young and growing plants,<sup>4d</sup> its presence in milk, human and animal,<sup>11</sup> and the absence of a relationship between the copper content and the geographical distribution of corresponding food materials<sup>4b</sup> are some of the conditions which suggest that its presence in biologic material is of fundamental importance.

## PATHOLOGIC SIGNIFICANCE OF COPPER

Can excess quantities of copper do harm? Mallory, Parker and Nye<sup>7</sup> first suggested that hemochromatosis was due to chronic copper poisoning. Chronic poisoning with the salts of copper produced in rabbit livers changes comparable in many ways with those found in

6 Malloy, F. B. *Am J Path* **1** 117, 1925

7 Malloy, F. B., Parker, F., Jr., and Nye, R. N. *J M Research* **42** 461, 1921

8 Severy, H. W. *J Biol Chem* **55** 79, 1932. Vickery, H. B., and Osborne, T. B. *Physiol Rev* **8** 393, 1928

9 Waddell, J., Steenbock, H., Elvehjem, C. A., and Hart, E. B. *J Biol Chem* **77** 777, 1928, **83** 251, 1925. Titus, R. W., Cave, H. W., and Hughes, J. S. *ibid* **80** 565, 1928

10 Bodansky, M. *J Biol Chem* **48** 361, 1921. Sheldon and Ramage<sup>3</sup>

11 Supplee, G. C., and Bellis, B. *J Dairy Sc* **5** 455, 1922. Hess, A. F., Supplee, G. C., and Bellis, B. *J Biol Chem* **57** 725, 1923

hemochromatosis in man. From a study of clinical records, Mills,<sup>12</sup> while working with Malloy, concluded that chronic poisoning with copper may be the cause of hemochromatosis. Particular attention was paid in this study to the possibility of exposure of the patients to copper. Analysis of the data, however, shows that though they are suggestive, they are not convincing, nor are Mallory's chemical data convincing. Six livers were analyzed with respect to their copper contents. In the first two organs examined (A22 64, A22 67) no copper was found, but the statement is made that "examinations were made by a cruder method which would not show minute amounts." The data obtained in the remaining cases were not unlike those found in four "control" cases. No mention is made of the chemical methods employed. As will presently be shown in the report of our case, this is an important consideration in the interpretation of results. The absence of a causal relationship between hemochromatosis and chronic copper poisoning is suggested from experiences with Koreans. The latter, as R. G. Mills pointed out,<sup>13</sup> numbering about 17,000,000, are continually exposed to copper, brass is the universal material out of which they manufacture the rice and other food bowls, spoons, etc. Brass is also used for wine bottles and some of the stills for making fermented liquors. Food not only is carried in brass vessels, but also is cooked in them and kept in them from meal to meal. The nature of some of the foods is such that they would exert a solvent action on the metal. The ingestion of copper begins shortly after birth and continues until death. In spite of this, Mills was unable to find any disturbance of pigmentation in 100 autopsies. Diabetes, a condition commonly associated with hemochromatosis, is also rare among these natives, the incidence found was about 0.1 per cent among hospital records. These observations fit with those of Flinn and von Glahn,<sup>14</sup> who were unable to confirm Mallory's experimental findings, copper and its compounds did not cause the deposition of pigment in the livers of rabbits or other animals used, and the feeding of a diet of carrots exclusively caused deposition of a pigment in the livers of rabbits in every way identical with that ascribed to copper.

Limited significance is apparently attached to copper as an industrial poison among workers in the United States.<sup>15</sup> The ill health found among copper miners or workers with the metal is largely attributed

12 Mills, E. S. Hemochromatosis with Special Reference to Its Frequency and to Its Occurrence in Women, *Arch. Int. Med.* **34** 292 (Sept.) 1924.

13 Mills, R. G. The Possible Relation of Copper to Disease Among the Korean People, *J. A. M. A.* **84** 1326 (May 2) 1925.

14 Flinn, F. B., and von Glahn, W. C. *J. Exper. Med.* **49** 5, 1929.

15 Hamilton, A. Industrial Poisons in the United States, New York, The Macmillan Company, 1925.

to other environmental conditions (heat, overexertion, irritating dust and the presence of lead or arsenic) Brass poisoning, brass founder's ague, is, according to the consensus, caused by the zinc in the alloy and not by the copper.

In spite of the conflicting data, there is reason to believe that excess quantities of copper may be harmful. It is rather difficult to reconcile the aforementioned views of workers in industrial poisoning with the "brassy" taste, the green line on the gums and the green discoloration of the sweat frequently found among workers in copper mines, nor are the views held by American authorities generally accepted. Until recently, the amount of copper allowed in foods in England was limited to 2 grams (0.13 Gm.), copper sulphate, hydrous ( $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ ) a pound. Under the new (1925) regulations, the addition of copper salts is entirely prohibited.<sup>16</sup> It is of interest to note that though no hemochromatosis was found among the Koreans, cirrhosis of the liver is common and is found frequently in young persons below the age of

TABLE 1—Results of Analyses in Twenty-Two Cases

Number of cases	Cirrhosis			No Cirrhosis		
	Maximum	Minimum	Average	Maximum	Minimum	Average
Milligrams of copper per kilogram of fresh material	85.6	2.9	20.8	9.9	0.6	5.4
Total milligrams of copper per organ	117.0	3.31	35.5	21.39	0.72	11.3

15 years. R. G. Mills suspects that this is due to chronic copper poisoning. The data of Cherbuliez and Ansbacher<sup>17</sup> are of interest here. These authors recorded analyses of the livers of 9 patients without, and of 13 patients with, cirrhosis. In each case are recorded the weight of the liver and the milligrams of copper per kilogram of fresh material. From these data, it is obviously possible to determine the maximum, minimum and average values and to calculate the total amounts of copper found in the different organs. Table 1 gives a summary of these calculations.

The foregoing finding of more copper in the liver in cirrhosis than in the control cases is not an isolated experience and suggests an etiologic relationship between copper and this condition of the liver. Unfortunately, exact comparisons of the different values obtained by different observers are not possible, because of the different values recorded. For example, some authors record milligrams of copper per kilograms of dry tissue, but fail to record the water contents of the organs, others

16 Cox, H. E. Chemical Analysis of Foods, London, J. & A. Churchill, 1926.

17 Cherbuliez, E., and Ansbacher, S. Arch. f. klin. Med. **278** 365, 1930.

record milligrams of copper per kilograms of fresh tissue and fail to state the total weight of the organs. Approximate comparisons, however, may be made in many cases when the total weights of organs are given, by assuming that the liver contains approximately 75 per cent of water. This value is in accordance with recorded analyses<sup>18</sup> and with our own. With the foregoing assumption, there is remarkable uniformity with respect to the average copper contents of "normal" livers. The observations have, therefore, prompted the report of the following case.

#### REPORT OF CASE

*History*—A deeply jaundiced man, aged 48, a laborer, was admitted to the medical service of one of us (A. H. G.) on May 25, 1932, in a semi-comatose state, with the following history. During the last fifteen years he had apparently suffered from some gastro-intestinal condition, consisting of eructations of gas that came on about one and one-half hours after meals and occasional vomiting. During the last year, he complained of pain in the epigastric region, which came on about one-half hour after each meal and was relieved by bismuth preparations. The jaundice gradually increased in intensity and dated from about five weeks prior to admission, however, there was also a history of occasional slight attacks during the last fifteen years. He had lost about 1 pound (0.5 Kg.) a day since the onset of the jaundice, but had continued to work until five days before admission, when he became drowsy. Clay-colored stools were frequently noted. The history was otherwise irrelevant, except that he had worked in a copper mine about fifteen years previously, and his illness apparently dated from that period.

The family history was irrelevant.

*Examination*—On admission, the physical findings were essentially negative, except for the jaundice, fluid in the peritoneal cavity and a definitely diminished area of dulness of the liver.

The laboratory findings were as follows. Two urinalyses were made. The specific gravities were 1.012 and 1.010, respectively, and at both examinations, large amounts of albumin, bile and bile-stained casts were found. There were also a few pus cells.

The contents of the stomach showed occult blood and an absence of free hydrochloric acid.

The stools were clay-colored and contained no blood.

The blood findings were as follows: red cells, 4,250,000, white cells, 5,700, hemoglobin, 85 per cent, smear, normal, and Wassermann reaction, negative.

On May 26, chemical analysis showed urea nitrogen, 22 mg per hundred cubic centimeters, creatinine, 1.5 mg, amino-acid, 7.5 mg, sugar, 0.169 per cent (not fasting), van den Bergh, 11.2 mg of bilirubin per hundred cubic centimeters of blood (28 units).

On May 30, chemical analysis showed urea nitrogen, 35 mg per hundred cubic centimeters, creatinine, 2 mg, sugar, 0.147 per cent, van den Bergh, 13.6 mg of bilirubin per hundred cubic centimeters of blood (34 units). Examination showed a trace of urobilinogen.

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<sup>18</sup> Wells, H. G. *Chemical Pathology*, ed. 5, Philadelphia, W. B. Saunders Company, 1925.



The following clinical note was made by one of us (A H G) on May 27

"The picture is that of yellow atrophy, but the duration of the illness is rather long. The absence of an alcoholic history and absence of engorgement of the abdominal and facial veins are strongly against the classical Laennec cirrhosis. A form of liver atrophy going on to fibrosis—so-called toxic or infectious type of hepatic cirrhosis—more nearly fits the case."

*Course*—From the time of admission of the patient to the hospital, there was a downward progress, he became rapidly comatose, and food was confined to intravenous injections of dextrose. The temperature tended to be subnormal, ranging from 96.4 to 98 F, with an average of 97 F. The patient died on June 2, eight days after admission.

*Autopsy*—An autopsy was performed eight hours after death, and the post-mortem diagnosis was yellow atrophy of the liver, exudative cholangitis with marked bile stasis.

As soon as the liver was removed from the body, it was weighed and examined grossly. A portion was removed for examination by the pathologist, and the remainder was sent to the metabolism laboratories for chemical analyses.

*Report of Pathologist (Dr L J Rhea)* The liver showed a marked and uniform reduction in size, weighing only 680 Gm. It was flabby in consistency. The capsule was wrinkled, especially near the thin, sharp, anterior border. The general color of the liver tissue was reddish yellow. Scattered throughout the liver were rather widely separated, rounded and definitely circumscribed yellow nodules. These scattered nodules projected as small eminences on the surface beneath the capsule, but, being widely separated and relatively few in number, the greater part of the surface of the liver was free from nodules. The architectural markings as seen on the cut surface were suggestive of a general collapse resulting from widespread destruction of the glandular tissue of the liver. The nodules were interpreted as areas of regeneration of the liver tissue.

Microscopic examination of sections taken from various parts of both lobes of the liver showed the general architecture to be markedly disturbed. Little traces of the normal lobular structure remained. All sections showed widespread areas of complete or almost complete necrosis, areas of fibrosis with bile duct proliferation and hyperplastic nodules of regenerated liver tissue. The increase in fibrous tissue was partly an apparent increase due to destruction of the glandular tissue with collapse of the lobule, but there was also a true increase in fibrous tissue. There was evidence of a widespread cholangitis. The fibrous bands, in which the proliferating bile ducts lay, were densely infiltrated by large numbers of lymphocytes and smaller numbers of polymorphonuclear neutrophils. The lumens of many of the bile ducts contained "pus cells." The occurrence of marked retention of bile, apparently resulting from the cholangitis, was indicated by the presence of yellow bile pigment lying free in the areas of necrosis, within macrophages in the fibrous bands, in the epithelial cells and lumens of the bile ducts and in the polygonal cells and distended bile canaliculi of still intact liver cords. In many places traces of the original lobular structure were to be seen in the form of small, collapsed, completely necrotic lobules outlined by fibrous bands containing proliferating bile ducts. Otherwise, there was no evidence of the normal lobular structure. Frozen sections stained with scharlach R did not show any excessive deposition of fat in the liver.

*Chemical Analyses* A portion of the liver was minced, weighed and dried to a constant weight in order to determine the water and solid contents. A portion

of the dried material was used for an estimation of the fat content. The results were as follows:

Weight	680 Gm
Water content	84.3 per cent
Total solids	15.7 per cent
Fat (Soxhlet extraction)	2.6 per cent
Fat-free solids	13.1 per cent

It will be observed that, compared with the normal liver, the water content was increased, but the fat content was within the normal limits. The liver, therefore, differed from that generally found in chloroform and phosphorus poisoning and fatty degeneration in general, in which the fat content may represent as much as 25 per cent or more of the total weight of the organ.

**Copper Analyses** A brief reference is here necessary to copper analyses in general, since, as stated before, the interpretation of the data depends largely on the technic employed.

Within recent years, because of the general recognition of the possible physiologic rôle of copper, chemists have been obliged to find more sensitive methods for both the detection and the quantitative estimation of minute amounts of this metal. A number of methods have been developed, each of which is quantitative providing due consideration is given to the various technical details, and selection of the method from those available is based on the amounts of copper in the material, as follows:

Method	Amount of Copper (Mg)
1 Chromotropic	0.002-0.10
2 Carbamate	0.010-0.050
3 Rhodamine-pyridine	0.050-0.100
4 Xanthate	0.100-0.200

It will be observed that as little as 0.002 mg can be measured. As little as 0.1 mg can be estimated with a high degree of accuracy. A variety of precautions is necessary for quantitative work.

The foregoing procedures apply to copper in inorganic form and in simple solution. Regardless of the method, therefore, a preliminary necessary procedure is the destruction of organic material. The two chief dangers at this stage are loss of copper or the addition by contamination. The necessary precautions have been dealt with elsewhere.<sup>19</sup> Of the two methods available, dry and wet digestion, the latter, at least in our experience, is preferable. Suitable dilution of the clear solution obtained after oxidation of the organic material, prior to the application of the different methods, makes possible the use of all the aforementioned methods. It is our practice to use the average value obtained from 3 methods. In the analysis of the liver in this case, the following results were obtained:

Method	Mg of Copper per Kilogram of Fresh Material
Xanthate	185.3
Carbamate	178.6
Rhodamine-pyridine	174.2
Average	179.3

<sup>19</sup> Ansbacher, S., Remington, R. E., and Culp, F. B. *J. Indust. & Engin. Chem.* **3**, 314, 1931.

As far as could be ascertained from the literature, the amount found in this case per unit weight and fresh material is the largest on record. Because of this finding, 4 other organs obtained from autopsies were examined. The amounts found were well below those found in this case of yellow atrophy (table 2).

In view of the intimate association between copper and arsenic in metals in general and in view of the well recognized causal relationship between arsenic and liver degeneration, it was considered advisable to analyze the liver in this case with respect to arsenic. The procedure used was standard and conformed in all details to our routine in toxicologic analysis, the organic matter was destroyed by the Fresenius-von Babo method, the mixture was then diluted with hot water treated with dilute sulphuric acid and filtrated. The clear filtrate was heated to expel excess hydrochloric acid and treated with arsenic-free hydrogen sulphide. The precipitate obtained with the latter (not necessarily arsenic) was extracted with ammonia and yellow ammonium sulphide, and the filtrate was tested for

TABLE 2—*Results of Analyses in Four Autopsy Specimens*

Autopsy No	Diagnosis	Weight of Liver, Gm	Mg. of Copper per kg. of Fresh Material
A 32 131	Carcinoma of the lung	1,650	11.2
A 32 133	General pyogenic infection, probably of pelvic origin	3,320	1.9
A 32 135	Tuberculosis	1,600	26.4
A 32 136	Tetanus	1,770	2.3
	Average		10.4

arsenic by the Marsh technic. No arsenic was found. In order to determine whether extremely minute amounts of arsenic might be present, the Gutzeit colorimetric method was used.<sup>20</sup> No arsenic was found.

#### RESUME

The literature on the metabolism of copper is briefly reviewed, and though the data are not conclusive they do suggest that copper, a normal constituent of food, may be harmful when administered in excess quantities.

A case of acute yellow atrophy of the liver is reported in which the liver was found to contain an enormous amount of copper. In spite of the large amount of copper, there was no arsenic. Though it may be difficult to associate the anatomic findings in the liver with the exposure of the patient to copper as long as fifteen years ago, there is a reasonable chemical basis for this association. There is, first, the incontestable fact that the liver contained a large amount of copper—as far as we could ascertain, the largest amount on record. It is suggested that the failure of the liver to excrete the copper may have been due to the fact

<sup>20</sup> Scott, W. W. Standard Methods of Chemical Analysis, New York, D. Van Nostrand Company, Inc., 1927.

that copper forms with protein a series of quite stable proteinates (The blue copper-containing protein of octopus blood, hemocyanine, is an example) The liver is also rich in products of protein digestion, many of which also form with copper quite stable compounds This fact is frequently made use of in quantitative analysis For example, the relative insolubility of the compound formed by copper and aspartic acid serves commonly for the estimation of this acid

The purpose of reporting our case is to prompt further investigation, in view of the present widespread and increasing use of copper therapeutically Though copper may have its use, its too general use might do harm An analogy is suggested in the experiences with the incorporation of iodine in table salt for the prevention of goiter

# DISTENTION AS A FACTOR IN INTESTINAL OBSTRUCTION

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The voluminous literature on intestinal obstruction has been adequately reviewed by Cooper<sup>1</sup> and Ochsner.<sup>2</sup> Although a toxemia is still generally regarded as the cause of all symptoms, a small group has dissented from this view and presented experimental evidence to show that death from high intestinal obstruction is probably due to nontoxic factors such as dehydration, decrease in blood volume, loss of electrolytes, loss of something specific in the gastro-intestinal secretions or alkalosis. The evidence for this point of view rests among others, principally on the work of Hartwell and Houget,<sup>3</sup> White and Bridge,<sup>4</sup> Burgess, Walsh and Ivy,<sup>5</sup> Jenkins,<sup>6</sup> White and Fender,<sup>7</sup> Armour and his co-workers<sup>8</sup> and Elman and Hartman,<sup>9</sup> all of whom have shown pro-

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1 Cooper, H S F The Cause of Death in High Obstruction, Arch Surg **17** 918 (Dec ) 1928

2 Ochsner, A Acute Intestinal Obstruction, Surg, Gynec & Obst **52** 702, 1931

3 Hartwell, J A, and Houget, J P Experimental Intestinal Obstruction in Dogs with Especial Reference to the Cause of Death and the Treatment by Large Amounts of Normal Saline Solution, J A M A **59** 82 (July 13) 1912

4 White, J C, and Bridge, E M Loss of Chloride and Water from the Tissues and Blood in Acute High Intestinal Obstruction, Boston M & S J **196** 196, 1927

5 Burgess, J P, Walsh, E L, and Ivy, A C Prolongation of Life of Dogs with Experimental Intestinal Obstruction, Proc Soc Exper Biol & Med **25** 105, 1927

6 Jenkins, H P Prolonging Life in High Obstruction by Administration of Salt Solutions Below Point of Obstruction, Proc Soc Exper Biol & Med **28** 111, 1930

7 White, J C, and Fender, J A The Cause of Death in Uncomplicated High Intestinal Obstruction, Arch Surg **20** 897 (June) 1930

8 Armour, J C, Brown, T G, Dunlop, D M, Mitchell, T C, Searls, H H, and Stewart, C P Studies on High Intestinal Obstruction, Brit J Surg **18** 467, 1931

9 Elman, R, and Hartman, A F Experimental Obstruction of the Terminal Duodenum and Ileum, Surg, Gynec & Obst **53** 307, 1931

longation of life by restoration of the salt and water volume in animals with experimental obstruction. White and Budge have found that the loss of chloride in the blood parallels a loss in the tissues. Survival brought about by reinjection of vomited secretions (Jenkins, White and Fender) or by relieving the obstruction with retention of the intestinal contents (Raine and Perry)<sup>10</sup> is, of course, opposed to the idea of toxemia. The work of Dragstedt and his co-workers<sup>11</sup> on loss of the digestive fluids also supports this point of view. None of these investigators deny the possibility of a toxemia in case the obstruction is complicated by strangulation, necrosis or peritonitis.

In actual obstruction, or in its counterpart by closed intestinal loops, the hydrostatic pressure of the accumulating fluids brings about considerable distention. This important factor, the subject of the present research, has received attention from relatively few investigators. Van Zwahlenburg<sup>12</sup> showed that intra-intestinal pressures of 90 mm of mercury delayed the flow in all the blood vessels, but that it took a pressure of 130 mm to stop the circulation. Dragstedt, Lang and Millet<sup>13</sup> found that the order of sensitiveness to intra-enteric pressure was duodenum, jejunum and ileum, and that a pressure of 80 mm of mercury reduced the jejunal blood flow to around 60 per cent. Sweet, Peet and Hendrix<sup>14</sup> looked on this distention and consequent rupture as the cause of death. Dragstedt, Dragstedt, McClintock and Chase<sup>15</sup> believed that distention made the intestinal wall permeable to the toxins found in the lumen as the result of bacterial action on proteins or their split products. In later papers, Dragstedt<sup>16</sup> attributed the toxemia and decrease in blood chlorides to the distention of the closed segments. The mechanism suggested was the powerful secretagogue action of the toxic fractions accompanied with a failure of reabsorption.

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10 Raine, F, and Perry, M. C. Intestinal Obstruction, *Arch Surg* **19** 478 (Sept.) 1929

11 Dragstedt, L. R., Montgomery, M. L., Matthews, W. B., and Ellis, J. C. Fatal Effect of the Total Loss of Gastric Juice, *Proc Soc Exper Biol & Med* **28** 110, 1930. Dragstedt, L. R., and Ellis, J. C. The Fatal Effect of the Total Loss of Gastric Juice, *Am J Physiol* **93** 407, 1930.

12 Van Zwahlenburg, C. V. Strangulation Resulting from Distention of Hollow Viscera, *Ann Surg* **46** 780, 1907.

13 Dragstedt, L. R., Lang, V. F., and Millet, R. F. The Relative Effects of Distention on Different Portions of the Intestine, *Arch Surg* **18** 2257 (June) 1929.

14 Sweet, J. E., Peet, M. M., and Hendrix, B. N. High Intestinal Stasis, *Ann Surg* **63** 720, 1916.

15 Dragstedt, L. R., Dragstedt, C. A., McClintock, J. T., and Chase, C. S. Intestinal Obstruction. II. A Study of the Factors Involved in the Production and Absorption of Toxic Materials from the Intestine, *J Exper Med* **30** 109, 1919.

16 Dragstedt, L. R. Blood Chemistry in Intestinal Obstruction, *Proc Soc Exper Biol & Med* **25** 239, 1928. Dragstedt, Lang and Millet<sup>13</sup>

Raine and Perry,<sup>10</sup> working on rabbits, believed that distention increased intestinal peristalsis and secretion and diminished reabsorption. Although they did not exclude toxemia, they attributed most of the symptoms to a loss of sodium chloride. Recently Burget,<sup>17</sup> has attached closed intestinal loops to the anterior body wall where they can be reached by the hypodermic needle. If the pressure is kept down the animals survive, but if distention is allowed to occur, there is vomiting, refusal of food, rupture of the loop and death from peritonitis. The changes in the chemical composition of the blood are relatively unimportant.

The purpose of the present investigation has been to find the cause of the symptoms and fatal outcome which follow a known distention of the intestine when uncomplicated by strangulation, rupture, necrosis or peritonitis.

#### EXPERIMENTAL PROCEDURES

With surgical asepsis, Thiry, Thiry-Vella and modified Thiry fistulas were made in dogs, the continuity of the intestine being reestablished by lateral anastomosis. In the modified type the intra-abdominal end of the fistulous loop was left attached to the upper portion of the jejunum, thus allowing the secretion of the loop to return to the main intestinal tract. All of these loops were taken just below the ligament of Treitz, which at autopsy proved to be about 40 cm from the pylorus. The loops ranged in length from 15 to 30 cm. In some cases biopsy samples of skin, muscle and intestine were taken for chloride and water analyses. The dogs were not used for the distention experiments until the wound was completely healed, the appetite good and the general condition thrifty. Throughout the experiment the dogs were allowed milk and biscuits ad libitum.

The fistulous loops were distended by inserting a balloon which was fastened to a suitably bent glass tube. The distention began about 4 cm from the external opening and extended for about 12 to 14 cm. The balloons were inflated with an air pressure of from 75 to 80 mm of mercury. This pressure was applied daily and in some cases oftener. Between times the pressure gradually fell, but it was not allowed to go below 50 mm before the next application. In the case of the Thiry fistulas, a small catheter was fastened along the side of the balloon to permit the secretions to escape.

All of the blood examinations were made before the distention experiment began and repeated again at the end. Blood for hemoglobin, erythrocyte and leukocyte estimations was drawn from the marginal vein of the ear after causing a good circulation by rubbing. Blood for alkali reserve, total chloride, nonprotein nitrogen and plasma chloride determinations was drawn from the femoral artery. Blood volume determinations were made according to the Whipple method as outlined by Rowntree, Brown and Roth.<sup>18</sup> Blood was drawn, and brilliant vital

17 (a) Burget, G. E., Martzloff, K., Suckow, G., and Thornton, R. C. B. The Closed Intestinal Loop. I. Relation of Intraloop (Jejunum) Pressure to the Clinical Condition of the Animal, *Arch Surg* **21** 829 (Nov.) 1930. (b) Burget, G. E., Martzloff, K., Thornton, R. C. B., and Suckow, G. R. The Closed Intestinal Loop. II. Observations on Dogs with Jejunal and Ileal Loops and Chemical Analyses of the Blood, *Arch Int Med* **47** 593 (April) 1931.

18 Rowntree, L. G., Brown, G. E., and Roth, G. M. The Volume of the Blood and Plasma in Health and Disease, Philadelphia, W. B. Saunders Company, 1929.

red was injected by way of the internal jugular veins Hemoglobin was determined by the Newcomer method, blood or plasma chloride by Whitehorn's method, tissue chloride by Van Slyke's method, nonprotein nitrogen by the micro-Kjeldahl method on the blood filtrate and the alkali reserve by the usual Van Slyke and Cullen procedure

These methods for studying the distention factor of obstruction, we believe, offer advantages over those used by other investigators The surgical procedures are separated from the experimental There is no accumulation of intestinal contents, either secretions or food residues There is no interference with the digestive functions of the rest of the alimentary tract There is no accumulation of fluid in the distended loop since its contents may either drain exteriorly or back to the normal intestine, according to the type of fistulas The distending pressure can be regulated The secretions may be collected and their rate of formation and nature be determined Through the modified loop, injections may be made into the normal alimentary canal The experiments can be terminated at any stage of the clinical picture, and they may be repeated on the same animal

#### SYMPTOMS AND BLOOD CHANGES SIMILAR TO ACUTE INTESTINAL OBSTRUCTION PRODUCED BY DISTENTION

If distention is a fundamental etiologic factor in acute obstruction, it is necessary to show that experimental distention gives the same general clinical and blood picture as obstruction itself To settle this point we have performed twenty-five experiments on fifteen dogs with Thiry fistulas and eight experiments on seven dogs with Thiry-Vella fistulas The two groups responded in exactly the same manner to distention and need not here be further separated from each other Of the twenty-two dogs, fourteen were allowed to run a fatal course, the average length of life being eight days The earliest death occurred on the fifth day and only one lived beyond ten days, dying on the fourteenth After inflation there is soon depression of activity, in some cases retching or vomiting, and by the fourth day, on the average, entire disappearance of appetite As distention continues, the dog shows loss of weight with signs of emaciation The coat loses its gloss and the skin becomes dry and inelastic The muzzle becomes dry and warm, the eyes shrunken and the pulse rapid Fibrillary tremors and weakness appear in the limbs, and the reflexes are depressed The temperature decreases one or two degrees, and a leukopenia may be found The animal shows no sign of pain but gradually passes into coma followed by death

The blood changes in the foregoing animals are shown in table 1 For the sake of brevity, five are given in detail and averages for the remainder The results are of interest in showing the widespread effects following increased hydrostatic pressure in an isolated loop The blood changes that have received most attention in intestinal obstruction are the fall in chloride, the rise in nonprotein nitrogen and the increased carbon dioxide content In our experiment the blood never failed to



show a decrease in chloride. This drop in blood chloride is not due to a decrease in per cent of plasma, because the chloride concentration of plasma is also reduced. This shows that there is an actual loss of chloride, just as in complete obstruction. The nonprotein nitrogen rose in all cases, the increase being most marked toward the end of the animal's life. The carbon dioxide-combining power in distended loops does not change greatly. An increase is usually found in those animals which show more or less vomiting and a slight decrease in some of the others, which is probably related to the ketosis from reduced food intake. In addition to these three cardinal symptoms, previous workers have generally believed there was dehydration as evidenced by hemoglobin

TABLE 1—*Blood Changes in Animals with Distention of Thy or Thy-Vella Loops*

		Blood							Plasma			
Ex- peri- ment No	Procedure	Weight, Kg	Hemo- globin, Gm	Red Blood Cells, Mil- lions	Vol- ume, Cc	Vol- ume in per Cent of Weight	NaCl, Mg per 100 Cc	Non- protein Nitro- gen, Mg per 100 Cc	Alkali Re- serve, Cc	Vol- ume, Cc	NaCl, Mg per 100 Cc	Plasma, per Cent
43	Normal	18.82	13.0	6.85	2,174	11.5	429	34.2	45.7	1,175	627	53.2
	Distention	14.62	17.0	10.06	1,441	9.8	379	39.3	40.5	585	561	40.6
51	Normal	11.30	10.5	5.75	1,186	10.5	495	29.1	40.0	676	610	57.0
	Distention	10.28	14.0	7.25	846	8.2	445	40.0	39.0	495	577	58.5
46	Normal	16.36	12.3	7.59	1,435	8.7	478	30.0	42.8	828	618	57.7
	Distention	13.20	14.2	9.49	1,266	9.6	396	12.9	51.3	740	705	55.7
50	Normal	13.50	14.0	9.67	1,123	9.3	462	29.5	46.4	621	610	55.3
	Distention	11.34	14.5	12.23	911	8.0	330	93.5	52.3	406	495	44.6
40	Normal	12.10	13.8	8.37	1,217	10.0	429	53.8	51.6	596	594	49.0
	Distention	9.88	19.0	10.09	910	9.2	297	70.5	49.0	325	465	35.7
Average changes in per cent		-15	+30	+33	-19		-24	+103	+11	-24	-17	-16
Number of ex- periments		15	16	13	11		21	21	12	11	5	10

determinations and hematocrit readings. Our animals have shown hemoglobin concentration, an increased red cell count and a decreased plasma percentage. In addition, by direct determinations of blood volume we have invariably found a quantitative decrease in plasma volume. The total blood volume also decreased from 12 to 34 per cent, with two exceptions in which it remained approximately normal.

In dogs with distended loops the total excretion of urea as well as total nonprotein nitrogen in the urine increases until near the end, while the excretion of chloride steadily falls. The quantity of urine remains more or less normal since the water consumed is absorbed by the intact gastro-intestinal tract.

In view of the fact that the symptoms and blood changes just described in our distention experiments are so much like those reported by all workers on acute intestinal obstruction, we believe we are justifi-

fied in assuming that the fundamental causes of the two conditions must be much the same. As further evidence, we have repeated our studies on three dogs with surgical obstruction made at the same level from which our loops were taken. The course in these dogs was exactly the same as that in our animals subjected to distention. The blood changes may be seen in table 2.

CAUSE OF DEATH FROM DISTENTION OF INTESTINAL LOOPS AND  
HIGH OBSTRUCTION

*Toxemia*—The idea that toxemia due either to bacterial or autolytic products was the cause of death in obstruction has been generally accepted because the clinical picture resembled that of known toxemias and because even recent experimentation has not given entirely clear-

TABLE 2—*Blood Changes in Complete Intestinal Obstruction*

Ex peri ment No	Procedure	Weight, Kg	Hemo globin, Gm	Red Blood Cells, Mil lions	Blood					Plasma		
					Vol ume, Cc	Vol ume in per Cent of Weight	NaCl, Mg per 100 Cc	Non- protein Nitro gen, Mg per 100 Cc	Alkali Re serve, Cc	Vol ume, Cc	NaCl, Mg per 100 Cc	Plasma, per Cent
34	Normal Obstruction	17.2	15.2	6.83			495	31.2	41.3			51.6
		14.7	17.4	7.25			297	187.5	47.3			55.3
59	Normal Obstruction	18.0	14.5	9.10	1,759	9.8	445	27.2	40.0	802	594	45.6
		16.7	17.5	10.27	1,529	9.1	247	99.9	49.0	575	495	37.6
61	Normal Obstruction	12.5	13.7	8.01	1,129	9.0	462	28.5	47.4	545	610	48.3
		11.0	15.0	8.70	910	8.2	313	51.9	51.3	488	429	53.6

cut evidence to the contrary. The relief of symptoms by injections of saline, reintroduction of vomitus below the obstruction, removal of the obstruction with the passage of the intestinal contents, or aspiration of a closed loop, convincing as these procedures at first seem, might all be explained by dilution, neutralization or withdrawal of a hypothetical toxin.

There are three features of our experiments which seem to exclude any possibility of a toxemia. The first of these was drainage of the loops. Mention has already been made that in distending the Thiry fistulas a tube was placed at the side of the balloon which allowed the secretions to flow to the exterior. Compared to the usual obstructions there was thus little material allowed to accumulate for bacterial action. To avoid the criticism that even a small amount of secretion at the bottom of the loop had putrefied and formed toxic products, the Thiry-Vella fistula was introduced, which allowed for drainage at the open end. Although this preparation excluded the possibility of any measurable retention of fluid whatever, the animals still succumbed.

To meet the objection that the death of these animals was really due to the formation of a very potent toxin in minute amounts, a second feature was introduced, namely, a modification of the Thiry fistula by leaving its distal end attached to the continuous intestinal tract. In these experiments, there was no loss of secretion to the outside. Any toxin, however, either bacterial or autolytic, should have been formed and absorbed as before, either in the distended area or in the region below, and death should have resulted even more promptly. These animals, however, proved entirely resistant. Three such animals, after enduring distention for sixteen, seventeen and nineteen days, respectively, remained in normal health and showed no significant blood changes. In one of these animals distention was performed a second time with similar results.

That these animals were not spared because of toxin neutralization in the parts below the loop, a criticism we have already made on previous work, was made evident by a third type of experiment, to be described more fully later, in which the Thiry fistula loop was denervated. Such denervated animals also proved resistant to distention, living indefinitely without any of the symptoms characteristic of obstruction or distention, yet if distended loops produced toxins it should have certainly occurred and the animals should have succumbed. Not only do these experiments seem to us to rule out the idea of a bacterial or autolytic toxemia in intestinal obstruction, but they also dispose of the theory that the intoxication might be due to the absorption of perverted or nondetoxified digestive secretions. Since the secretions of the stomach, pancreas, liver and Brunner's glands follow their normal course and yet the alleged toxic symptoms still appear on distention of unmodified Thiry and Thiry-Vella loops, there must be other causal factors. That there has been no perversion of the intestinal secretion in the loops themselves is shown by the two types of experiments mentioned in which toxic symptoms do not appear.

Autopsy was carefully performed on all dogs that died or were killed at the end of an experiment and in many cases the loop was examined histologically. If the loop showed rupture or there was any peritonitis, the results were discarded. Grossly, the distended segments showed loss of tonus, thinning of the walls, a deeper color than adjoining regions and occasionally some mucosal desquamation in small areas. Histologically, there was marked lymphocytic infiltration, hyperemia with some hemorrhage, and the thinning was seen to be due to loss of villi and mucosal glands. These anatomic changes did not seem sufficiently marked to suggest any form of toxemia from tissue breakdown, particularly since they were found both in animals that died as well as

those that survived Elman and Haitman<sup>9</sup> have described much the same changes in the intestinal wall above the obstructions

Being unable to find any evidence in support of the various theories of toxemia as a cause of the symptoms and death in distention and obstruction, we turned our attention to nontoxic factors

*Dechlorination, the Essential Change Following Distention*—The chief blood changes which have interested previous observers and to which a number have attributed all the signs and symptoms of obstruction are alkalosis, increased nonprotein nitrogen, dehydration and dechlorination Our next problem was to find which of these, if any, were responsible for the outcome in our own experiments duplicating high obstruction

Although the literature on obstruction generally emphasizes marked alkalosis as one of the cardinal symptoms, an inspection of the data presented does not entirely justify that conclusion Hayden and Oll<sup>19</sup> and Habler<sup>20</sup> all cite numerous experiments in which carbon dioxide-combining power showed great variability, often falling below normal The high values reported by Hastings, Murray and Murray<sup>21</sup> and Armour<sup>8</sup> and his co-workers seem exceptional, at least for jejunal obstructions

Alkalosis in itself did not seem related to the fatal outcome in our animals In twelve dogs the carbon dioxide-combining power of the arterial plasma averaged only 11 per cent higher than normal, the variations being about the same as those reported by many other workers Furthermore, a number of our animals showed either no change in carbon dioxide-combining power or an actual decrease, and yet they died in the usual manner with the blood changes typical in all other details Variability in our animals has a rather obvious explanation Vomiting is a constant symptom of clinical obstruction, and the loss of hydrochloric acid in the vomitus makes for alkalosis Distention of a short loop may or may not produce vomiting, and it is apt to be moderate if it occurs Our animals that did vomit were among those that showed increases in alkali reserve

Increased nonprotein nitrogen invariably occurred in all of our unmodified distention experiments The amount was often more than doubled, as may be seen in experiment 50 table 1 The lower figures are for samples of blood taken some time before death Urea itself in

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19 Hayden, R, and Orr, T G Experimental Obstruction of the Jejunum, J Exper Med **41** 707, 1921

20 Haebler, C Untersuchungen zur Molekularpathologie des experimentellen Dunndarmverschlusses, Ztschr f d ges exper Med **54** 524, 1927

21 Hastings, A B, Murray, C D, and Murray, H A Certain Chemical Changes in the Blood After Pyloric Obstruction in Dogs, J Biol Chem **46** 223, 1921

two of our experiments increased, 100 and 300 per cent. Later analyses were always markedly higher, which shows that the formation or retention of nonprotein nitrogen is a late event in the picture. All the other symptoms are already well developed, which we believe is a point of importance.

In interpreting a rise in nonprotein nitrogen one must consider necrosis, blood concentration, scanty secretion of urine and kidney damage. For necrosis, we have been unable to find any evidence, either grossly or histologically. As a matter of fact, there may be a good deal of tissue degeneration and absorption without a rise in blood nonprotein nitrogen, as shown in Dragstedt's experiments.<sup>15</sup> Blood concentration would of itself increase the percentage of nonprotein nitrogen in the blood.

TABLE 3—*Urine Excretion of Dog 13 with a Distended Thyro-Vella Fistula*

Date	Amount of Urine, Cc	Daily Chloride Excretion Urine and Juice, Gm	Nonprotein Nitrogen, Gm per 100 Cc	Total Daily Excretion, Gm
10/11/30	420	2.81	1.62	6.8
10/12/30	370	2.5	1.62	6.0
10/13/30	325	2.04	1.9	6.1
Inflated				
10/14/30	460	3.82	1.62	7.4
10/15/30	330	3.71	1.68	5.5
10/16/30	470	3.19	2.10	9.9
10/17/30	465	2.55	1.50	7.0
10/18/30	245	1.32	2.11	5.2
10/19/30	195	1.07	1.5	3.0
10/20/30	160	0.85	1.86	2.9

\* The dog weighed 15 Kg., it died on Oct. 20, 1930.

The resulting viscosity and reduced rate of circulation might impair renal response. That this is not the important factor is, however, shown by two facts. First, that the increase in nonprotein nitrogen outruns the blood's concentration, and second, there is a normal amount of urine and an actual increased excretion of nonprotein nitrogen until the terminal stage appears. The evidence for kidney damage is thus slight during the larger part of the experiment. The evidence for this argument may be seen in tables 1 and 3.

Since the increased nonprotein content of the blood does not seem to be a simple kidney retention phenomenon there seems to be no other alternative except to assume there is an increased production, the exact cause of which we do not know.

Whatever the cause of the increase in nonprotein nitrogen may be we do not believe it is the fundamental disturbance. The fact that it is a late event in the picture after all the other symptoms are well developed indicates that it is a result and not a cause.

Evidences of dehydration were present in nearly all of our animals. The usual decrease in blood and plasma volume may be seen in table 1, and this loss of water is reflected in the tissues, as may be seen in table 4. We had hoped to be able to separate the two factors, dehydration and dechlorination, but in only one animal has there been any evidence of such a possibility. Dog 50 was subjected to three periods of distention. In the first of these plasma volume decreased from 636 to 437 cc and chlorides fell only from 495 to 412 mg per hundred cubic centimeters at which time the period was terminated. In the second period plasma volume fell from 629 to 427 mg and salt from 484 to 412 mg. In these two experiments the animal showed no symptoms. In the third period the plasma volume dropped from 621 to 406 mg, about the same

TABLE 4—*Tissue Analyses for Chloride and Water*

	Biopsy		Necropsy	
	Water, per Cent	NaCl, Mg per 100 Gm	Water, per Cent	NaCl, Mg per 100 Gm
Dog 42				
Muscle	75.5	441	66.7	225
Skin	47.8	453	30.8	234
Intestine	71.2	686	72.2	225
Dog 43				
Muscle	71.2	410	72.9	374
Skin	64.8	508	57.3	477
Intestine	78.7	282	81.4	160
Dog 37				
Muscle	79.1	424	74.9	357
Skin	64.9	683	51.6	566
Dog 39				
Muscle	74.9	641	70.6	413
Skin	48.9	518	52.7	467

as before, but the salt was allowed to drop from 462 to 330 mg. At this time the animal showed all the symptoms of typical distention. The decrease in blood plasma being no greater in the third period, the result was naturally attributed to the low chloride content of the blood and tissues. Gamble and Ross<sup>22</sup> have also reported the loss of one dog in which there were no signs of loss of water but marked dechlorination. In view of the literature on edema, a decrease in chloride, no matter which ion is responsible for the effect, would ordinarily be associated with loss of water, and such we believe to be the usual case in the distention experiment.

Since vomiting was not sufficient to account for the loss of chloride in our animals, our attention was turned to the total loss in the urine and in the secretion from the fistula. In table 3, it may be seen that the total excretion of chloride at once increases on inflation of the loop

<sup>22</sup> Gamble, J. L., and Ross, S. G. The Factors in the Dehydration Following Pyloric Obstruction, *J. Clin. Investigation* 1: 403, 1925.

The figures are minimal, due to the difficulty of getting all the secretion from the fistula from the cage and from the animal's body. Since the appetite fails almost immediately in an experiment as short as this one, the loss of chloride after the second day is almost entirely uncompensated. By the time of death the animal had therefore actually lost about 12 Gm of chloride computed as sodium chloride. On the basis that normally he had about 2.5 Gm chloride per kilogram of body weight, his loss would represent about one third of his total, quite enough to bring about serious disturbances in bodily functions.

There is no mechanism apparent by which distention might cause the kidney to increase its excretion of chloride, and, as a matter of fact, workers generally report a decreased excretion of salt in the urine in obstruction. The obvious pathway for loss of salt in our experiments

TABLE 5—*Secretion of the Fistulous Loop*

Dog		Plasma NaCl, Mg per 100 Cc	Rate of Secretion per Hour, Cc	NaCl Content of Juice, Mg per 100 Cc
30	Normal	610	1.0	759
	Distention	544	8.0	697
40	Normal	596	1.0	759
	Distention	502	21.8	779
46	Normal	643	3.0	693
	Distention	511	7.1	577
43	Normal	627	1.2	462
	Distention	561	13.2	693
54	Normal	627	1.4	759
	Distention (denervated)	610	17.0	792
55	Normal	627	4.2	676
	Distention (denervated)	627	23.0	792

is the secretion from the distended loop, and this we have carefully studied in many animals. In table 5 we have collected data for several of these on the rate of secretion and salt content before and during distention. The latter is also compared with the plasma chloride. During distention the high rate of secretion and its richness in chloride is most striking and leaves no doubt as to the real source of chlorine and water loss. In extreme cases such as dog 40, over 500 cc of fluid may be secreted daily by a 15 cm loop of the upper portion of the jejunum. The salt in this amount would be 3.9 Gm. This particular dog weighed 12.5 Kg. His total salt content was about 30 Gm. There was a total of 5.3 Gm in his blood by actual determination. He therefore lost daily over 10 per cent of his total chloride and 74 per cent of his total blood chloride. It is obvious that life could not long continue without a greatly increased salt intake. Even with one of our two lowest rates of secretion, such as in dog 46, the loss of chloride amounts to 1 Gm per day.

That distention is a powerful stimulus to intestinal secretion is seen from these figures Lim, Ivy and McCarthy<sup>23</sup> have reported this mechanism for the stomach, but its part in intestinal obstruction, so far as we can find, has been overlooked. Increased hydrostatic pressure in obstruction has been generally regarded as due to an accumulation of the normal secretions, and it has been believed to lead to reabsorption rather than increased rate of secretion.

There are several reasons for thinking this output of intestinal juice is a true secretion and not a transudation because of pressure injury to the mucosa. It begins at once on the application of pressure. In dog 55 the determination of secretory rate immediately followed insertion of the balloon. It is for this reason that the two values for plasma chloride are the same. After five days of distention the increased secretion ceases within from four to six hours after removal of the balloon. Further evidence that the juice is not a transudate but a secretion is found in the fact that the chloride content of the juice is regularly higher than that of the plasma, and it may rise as the chloride content in the plasma falls. We have at present no explanation of this important fact. The juice at all times had the normal amount of invertase. This was determined by comparing the effect of juice from normal and distended loops on the hydrolysis of sucrose. The hydrolysis curves of the two juices were exactly similar. For all these reasons we regard the juice as essentially a true secretion.

As evidence that the losses of salt and water were of sufficient magnitude to be of real importance to the tissues, we have made analyses from biopsy and necropsy material. Skeletal muscle, skin and intestinal muscle all show losses in their salt content, sometimes as much as 50 per cent. The loss of water is greatest in the skin.

In animals that do not vomit, such as rabbits, a great collection of fluid is found in the contents of the distended intestine and stomach. This observation of Bunting and Jones<sup>24</sup> we have several times confirmed. In a rabbit weighing 2.4 Kg, 320 cc of fluid was found in the stomach and duodenum. That this fluid came in part from the animal's blood volume was shown by 100 per cent increase in hemoglobin. The chloride content of the fluid amounted to 1.8 Gm, which was nearly a third of the total body chloride. These results indicate that the cause of death from obstruction in rabbits is essentially the same as that from distention in our dogs.

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<sup>23</sup> Lim, R. K. S., Ivy, A. C., and McCarthy, J. E. Contributions to the Physiology of Gastric Secretion. I. Gastric Secretion by Local (Mechanical and Chemical) Stimulation, *Quart J Exper Physiol* **15** 13, 1925.

<sup>24</sup> Bunting, H. C., and Jones, A. P. Intestinal Obstruction in the Rabbit, *J Exper Med* **17** 192, 1913, **18** 25, 1913.



If our contention is correct that dechlorination is the important factor in death from distention, it should be easy to test the matter by transfusions of sodium chloride. Although the literature is conflicting on this point, a number of workers have reported successful experiments after obstruction, among whom are Haden and Ori,<sup>10</sup> Jenkins<sup>6</sup> and Aimou<sup>8</sup> and his co-workers. In our first attempt we transfused with 0.9 per cent sodium chloride whenever the hemoglobin showed increasing concentration. We hoped in this way to add salt and maintain blood volume. The dog endured distention eleven days in fairly good condition, which was evidence that the treatment was beneficial. After every injection there was, however, a marked increase in the amount of secretion from the fistula. It was evident that we were really defeating the purpose we had in mind and that the blood volume and its chloride content were being subjected to continual fluctuations. Furthermore,

TABLE 6—*Effect of Introducing 30 Cc of 10 Per Cent Saline Daily into a Second Fistula During Distention of a Thiry Loop in Dog 40*

Ex peri ment No	Procedure	Blood							Plasma		
		Weight, Kg	Hemo globin, Gm	Red Blood Cells, Mil lions	Vol ume, Cc	Vol ume in per Cent of Weight	NaCl, Mg per 100 Cc	Non protein Nitro gen, Mg per 100 Cc	Alkall Re serve, Cc	Vol ume, Cc	NaCl, Mg per 100 Cc
1	Normal	13.44	11.8	7.60	1,180	8.7	478	29.7	46.2	661	610
	Distention	11.50	13.3	7.07	1,009	8.7	478	27.1	47.4	505	579
2	Normal	12.46	13.0	7.32	1,182	9.5	453	31.8	47.6	623	585
	Distention	12.10	13.8	8.37	1,217	10.0	429	34.2	51.6	596	594

this experiment did not clearly show that chloride was the therapeutic factor, since blood volume was also increased.

We therefore decided to administer 10 per cent saline directly into the intestine. To do this we prepared dog 40 with two fistulas, one a Thiry and the second a modified Thiry, connected distally to the jejunum. While the animal was undergoing distention, 30 cc of salt was daily run into the second fistula. This dog endured two periods of distention of fourteen days each without symptoms of any kind. The fact that chloride without any significant amount of water maintained normal blood may be seen in table 6. As a control the dog was subjected to a third period of distention without the administration of salt. The disastrous effects during this period may be seen under experiment 50 in table 1.

*A Nervous Factor*—It was early noted that at the moment of distending a loop the animal often showed signs of nausea. This was followed by a temporary disinclination for food. Although the appetite temporarily returned, by the fourth day on the average a permanent

anorexia developed. The uncompensated loss of chloride from the loop which now resulted has already been emphasized. The appetite which determined the intake of food thus became very important, for if the dog were only eating enough he could, of course, make up for his loss of chloride. Since the appetite failed before the chlorides in the blood had greatly decreased, we were led to suspect that it was inhibited by sensory nervous stimulation from the loop. This loss of appetite Burget<sup>18a</sup> has also noted if the pressure were allowed to rise in his closed intestinal loops.

It is obvious that if an inhibition of the appetite prevented a sufficient intake of chloride, any removal of the inhibition would be of benefit to the animal. We therefore decided to denervate a series of animals with Thury loops. The arteries and veins of usual sized loops

TABLE 7—*Effect of Distention of Denervated Thury Fistulas*

Ex- peri- ment No	Procedure	Weight, Kg	Hemo- globin, Gm	Red Blood Cells, Mil- lions	Vol- ume, Cc	Blood			Alkali Re- serve, Cc	Plasma		
						Vol- ume in per Cent of Weight	NaCl, Mg per 100 Cc	Non protein Nitro- gen, Mg per 100 Cc		Vol- ume, Cc	NaCl, Mg per 100 Cc	Plasma per Cent
52	Normal	18.56	12.0	6.74	1,769	9.5	495	26.1	43.8	1,114	614	63.0
	Distention	17.50	10.8	6.20	1,354	7.7	519	30.0	43.8	853	643	63.0
54	Normal	13.28	12.5	7.04	1,200	9.0	495	29.7	43.9	706	627	58.9
	Distention	13.76	12.5	6.44	1,160	8.4	486	31.5	42.4	603	610	52.0
60	Normal	17.56	10.2	6.29	1,718	9.8	495	29.4	48.1	1,082	627	63.0
	Distention	18.56	14.0	8.56	2,035	10.9	478	28.5	49.2	1,038	610	51.0

were dissected entirely free of all surrounding tissue, the nerve strands being picked up and a wide segment removed to prevent regeneration. The artery and vein were then painted with full strength phenol, which was removed with alcohol and saline. The pedicle of the loop then consisted of nothing but the afferent and efferent vessels. We now have experiments on eight animals prepared in this way. Three of these endured distention twenty, twenty-one and twenty-three days without any symptoms, at which time the experiments were discontinued. The blood of each remained normal except for a shrinkage of volume in no 52. The data from these three dogs are shown in table 7.

Two dogs were without symptoms for a week, when the experiments were terminated in one case by distemper and in the other by an actual obstruction and rupture due to adhesions. One dog was without symptoms or blood changes for thirteen days, at which time an accidental rupture of the loop occurred. A seventh animal was without symptoms for eleven days, and then quit eating. There were no other symptoms, but the blood had definitely changed toward the obstructed

type The eighth dog showed no protection whatever, which we hope was due to a failure in denervation Of these eight dogs, three showed complete immunity to distention and four others undoubted protection All these animals showed high secretory rates on distention, the two latter animals, however, had the highest rates we have ever observed 30 cc per hour in one and 23 cc in the other We believe the high loss of salt in these cases was more than could be compensated for by a normal appetite and intake of food Sooner or later the usual symptoms had to appear

A study of these denervated animals has convinced us that anorexia due to stimulation from the distended loop is one of the fundamental factors in the development of dechlorination In distention not only is chloride lost by an increased loop secretion, but the intake is also curtailed Both the eating of salt and the administration of it, either by vein or by fistula, become devices for maintaining the body chloride

#### COMMENT

The introduction of isolated intestinal loops by Whipple and his co-workers<sup>25</sup> was the first important advance that has been made in the study of intestinal obstruction by experimental methods Outstanding as this procedure was, it still did not allow the various factors concerned in obstruction to be dissociated from each other We believe that our method of distending open fistulous loops accomplishes this necessary condition, and that for the first time, some of the factors can be studied independently

From the data presented, it is evident that distention of an isolated intestinal loop produces a train of symptoms identical with those observed in acute high obstruction, and since obstruction is regularly accompanied by distention, the symptoms in all probability have a common origin in the two conditions Our studies then have made it possible to follow the sequence of events both in distention and obstruction

There is no evidence of toxemia either from bacterial invasion or necrosis of intestinal tissue On the application of pressure the animals at once usually show some signs of restlessness and nausea, and vomiting may occasionally occur These reactions are temporary and usually disappear within a few hours The first permanent symptom to attract attention is a marked increase in the fluid flowing from the loop This seems to be a true secretion resulting from the mechanical stimulation of the loop, since it contains ferments common to those in succus enteri-

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<sup>25</sup> Stone, H B , Bernham, B M , and Whipple, G H Intestinal Obstruction A Study of the Toxic Factors, *Bull Johns Hopkins Hosp* 23 159, 1912

cus It is extremely rich in chloride, the daily excretion often being in excess of the animal's normal intake Although after the initial period obvious gastro-intestinal reflexes may be lacking, the animal is receiving sensory stimuli from the loop Whether these are conscious or subconscious can, of course, not be told There are no signs of pain but rather an appearance of general malaise The appetite slowly fails, and by the fourth or fifth day, complete anorexia supervenes A nervous factor once suggested but long since denied is thus seen to be of importance The output from the loop, amounting to several hundred cubic centimeters per day, is now entirely uncompensated so far as chloride is concerned Although the animal may still take water, it does not equal the amount lost through the secretions, respiration and insensible perspiration Both plasma and total blood volume now show decreases The plasma chloride content falls daily The hemoglobin and nonprotein nitrogen rise The tissues appear desiccated, and both desiccation and dechlorination are borne out by chemical analyses Of these two factors the dechlorination seems to be the more important By the time the plasma chloride has decreased 25 per cent on the average, the animal is in coma and death imminent Since the decrease of chloride in the blood and tissues is the one finding absolutely constant, and since restoration of blood chloride brings relief, it is believed to be the most important factor in causing death from experimental distention and acute high intestinal obstruction Death in all probability is due to changes in the electrolytic condition of the cells so marked that life itself is made impossible Distention of an intestinal segment may be the initiating cause of the whole train of symptoms

The authors are not in a position to make any extended comparison of their experimental procedures with clinical conditions, and only a few remarks need be made on this point In acute uncomplicated obstructions there is distention and loss of fluid and chloride into the bowel In animals the amount lost in this way is enough to lower the body fluids and chlorides below the danger point, and there is no reason for doubting that this occurs in human cases Since distention is in itself responsible for such a serious sequence of events, it is obvious that the reduction of the distending pressure above an obstruction is to be considered Maintenance of body fluids and their salt content must also be important therapeutic measures

Although the term "dechlorination" has been used throughout this paper, it is possible that the term "demineeralization" would be more appropriate While the evidence for a disturbance in the body chloride seems convincing, other electrolytes may also be concerned So far no distinction has been made among the various chlorides In addition, the loss of the cation of these salts must not be overlooked

## SUMMARY

1 By the distention of Thiry and Thiry-Vella fistulous loops of the upper portion of the jejunum all the symptoms of acute high intestinal obstruction may be reproduced. The advantage of this method lies in the avoidance of immediate operative effects and in the possibility it gives of isolating certain of the factors involved.

2 Constant distention of the loops with from 50 to 80 mm of mercury results in malaise, loss of appetite, excessive secretion from the loops, desiccation and dechlorination of tissues, decreased blood and plasma volumes, increased hemoglobin content, moderately increased alkali reserve, high nonprotein nitrogen and greatly decreased blood chloride. Death occurs on about the eighth day.

3 The evidence that death is not due to a toxemia seems conclusive. Drainage of all fluid from the loop exteriorly does not prevent a fatal outcome, but drainage back into the continuous intestine prevents symptoms from appearing. This precludes toxemia either from bacterial products or necrotic substances from the intestinal wall. Deneivated loops also withstand pressure, often with entire impunity.

4 Death is believed to be due primarily to the loss of chloride which is poured out by the loop under the stimulation of the mechanical pressure. This is almost invariably accompanied by decreased blood and plasma volume, but that the loss of chloride is the more important factor is evidenced by the fact that animals may be kept alive by introducing small quantities of 10 per cent salt directly into the intestine.

5 A nervous factor has been demonstrated in the train of symptoms. Dogs with deneivated loops may withstand pressure indefinitely. They do not lose their appetites and thus maintain their body chlorides even in the face of an exaggerated loss through the distended loop.

## Book Reviews

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**Special Cytology** Edited by E V Cowdry Second edition In three volumes  
Price, \$30 Pp 1,839, with 757 illustrations New York Paul B Hoeber,  
Inc, 1932

The "Special Cytology" has, after four years, appeared in a second and augmented edition, this new edition has been extended to include three volumes, whereas the first was confined to two, there are numerous additional illustrations, five hundred more pages (now totaling over eighteen hundred) and nine new sections Twenty-seven of the entire forty-four chapters have received little or no modification, seven have been considerably altered To produce this work, the assistance of forty-six contributors was sought—in itself an editorial task of imposing proportions, by it the English reader is brought handily to sources the separate collection of which would be an overwhelming labor

Each section conveniently carries its own table of contents and ends with a list of references, frequently imposing in length and abundant in selected items, there is a total of almost two thousand in the first volume alone

Many of the works cited were written within the last decade, yet there is more than a little truth in an introductory statement that modern cytology shows a gratifying tendency to revert to the earlier scheme of studying living cells (by microdissection and by examination of translucent tissue) In the present work there are reported original investigations on the physical consistency and the finer structure of the cells in untreated skin—their intercommunicating protoplasmic fibrils and granular mitochondrial elements Other recent studies on the skin are reported, which stress its importance as a manufactory for enzymes, hormones and antirachitic and immune bodies and its office as a whole membrane through which chemical substances pass en route to the circulation Modern histology thus turns back to a study of layers—of major interest a century ago

One is reminded that the nasal secretion was for ages considered an excrementitious humor distilled within the cerebral ventricles and passed into the nose and mouth through a cribose nasal roof The true source of this functionally important secretion—the mucous membrane—is fully described, and the cellular features contributory to its striking activity are carefully reviewed The discussion is not extended, however, to include the buccal or labial mucous membrane, which latter is still incorrectly described in textbooks despite the fact that Frederic Ruysch, as early as 1703, presented an admirable account of its peculiarities

The histology of the lower respiratory tract is described, and the nature of the alveolar epithelium is displayed by original preparations In the excellent chapters on the cytology of the alimentary tract and its glandular outgrowths, one finds a most serviceable group of figures, nearly one hundred in number, which display the various intracellular mechanisms, their elaborated products and the paths within the cell traversed by the latter, however, as the reader is cautioned, the time has not yet come when the investigator may with certainty state which substances within the active cells produce the physiologically recognized secretion, nor can a specific enzyme be discovered infallibly by a given microchemical method

About two hundred years ago a Fellow of the Royal College of Physicians in London recorded his perplexity regarding the functions of the spleen He put aside unequivocally the "variety of schemes" laid down from ancient times, and, finding, through extirpation in animals, that the organ was "unnecessary to individuals," he believed that it must be designed for some office in promoting the propagation of the species, since organs are not by nature contrived in vain! The contributor to the current work must still admit that "little is known concerning

the functions of the spleen," functional interpretation being inherently difficult whenever an organ's parenchymatous parts are not peculiar to it. A clear account, however, of histology of the spleen can be and is presented, and its relation to hematopoiesis is discussed. Five excellent sections follow on the formed elements of the blood, but, of the containing vessels, only the capillaries receive attention—and these in a closely written, lucid account. The endocrine glands are dealt with in four sections, the section on the pineal body is new, and replaces an earlier and much longer section which contained a great deal of interest in comparative anatomy and histology, the section on the suprarenal is almost wholly physiologic. The section describing the renal tubules makes clear not only the regional cytologic differences, but the comparative embryologic basis of these. Too little space is given than some textbooks allot to this important subject, and one which is the object of increasing clinical inquiry. Admitting that in an edited work, all chapters cannot be of equal value, it still seems that this account falls rather too far short of the standard set by certain European works of similar type. Synovial membranes are allotted a section, fortunately, one must admit, since the author states that there still exists the opinion "that joints and bursae are lined by endothelium." The several kinds of muscle are discussed, and the specialized systems of the heart are described in a convincing anatomic account which brings one again near the dependable older sources and points out recent errors in description.

The original chapter on the eye has been extended to include the choroid, the sclera and the pathologic changes in all the layers. The collection of figures of the visual elements in various vertebrates is unique and most valuable. The degree to which this and several other excellent chapters have been changed seems to be a measure of the individual author's painstaking effort to render his section not only a more inclusive account, but also a more accurate appraisal of the numerous investigations, rather than being "a rough measure of activity in the lines of research represented." A very good new chapter has been added descriptive of the cornea and the lens.

The internal ear, nerve cells, neuroglial elements and cerebrospinal pathway are discussed and a section on microdissection of the nerve cells has been added. The cytology of the uterine gland cells, the ovary, ovum and tubes, the cells in the vaginal fluid and the mammary gland are discussed by those who have contributed greatly to recent knowledge of these elements. The interstitial cells of the testis, the germ cells and the cytology of the seminal vesicles, prostate and bulbo-urethral glands are the closing subjects—all ably handled.

In general, it may be said that many of the cytologic figures suffer in not being reproduced in their original colors to display effectively the significant cellular tinctorial materials. There are few omissions, and doubtless they were purposeful and well considered, one may note the following: connective tissue proper, tendons, arteries, veins and lymphatics, the mucous membrane of the mouth, the lips, and the large and small intestines, serous membranes, the non-nervous labyrinthine epithelium, the lymph glands, the nails. It seems curious indeed that in such an extensive and modern work on cells, prepared almost three hundred years after Hooke first commented on cell-shape, no mention is made of the three-dimensional form of these fundamental units of bodily structure, yet the superb recent studies of cellular morphology, published by an American anatomist, are readily available to the editor.

Many of the contributors succeed in their attempt to integrate structure, normal function and deranged activity of the cells and the organs, and so not only provide informative and provocative narratives, but broaden the usefulness of the volumes. Many readers will not agree, however, that, without the inclusion of physiologic and pathologic discussion, the presentation would be "both sterile and uninteresting."

**Internal Medicine Its Theory and Practice in Contributions by American Authors** Edited by John H. Musser, B.S., M.D., F.A.C.P., Professor of Medicine in Tulane University of Louisiana School of Medicine, Senior Visiting Physician to the Charity Hospital, New Orleans Price, \$10 Pp 1316, with 16 tables and 39 illustrations Philadelphia Lea & Febiger, 1932

Whenever a textbook of medicine is published in this country, it is the natural instinct for many to contrast the new book with Osler's "Practice of Medicine." The appearance of Dr. Musser's volume compares not unfavorably with such a model. The first edition of Osler's work, which was published forty years ago, contained 1,050 pages of text, each page averaging around 500 words. The first edition of this new book contains 1,293 pages of text, each page averaging, also, around 500 words. The type is clear and easy to read, the paper is of good quality, so that the pages turn over comfortably, the book weighs only about 5 ounces more than its eminent predecessor, and it can be handled just as easily, is attractive looking and is of convenient shape and size. So much for the book's physical characteristics.

The new "Internal Medicine" is a textbook on theory and practice, covering the entire field of medicine. It is written by a group of twenty-seven well known American authors and is edited by one of them. The editor has been remarkably skilful in smoothing out the individual peculiarities of literary style among his contributors so that the reader is not irritated by abrupt changes in methods of presentation or expression on the different subjects discussed. The editor, too, has balanced the contents of his book most carefully, giving due space to subjects of general clinical interest and curbing the verbosity of his co-workers who have written about rare diseases. Thus, the importance of no single subject is over-emphasized or minimized.

Since each contributor is a teacher, thoroughly familiar with the ground he covers and well trained in the art of presenting medical facts in an interesting fashion, the entire book makes good reading. Some of the sections are necessarily very short, on the other hand, no space is wasted by useless charts, diagrams or words. The information put forth is expressed in concise, up-to-date English and the various methods of diagnosis and treatment that are advocated are sound and of established value.

The description of many diseases begins with a short historical narrative mentioning the important names and publications to be remembered as best recording the development of knowledge in regard to the subject under consideration, and each section ends with a few references to direct those interested into the way of more comprehensive reading. A good index completes the book.

On the whole, this new textbook is admirable. Teachers, students and practitioners will enjoy it, not only because it is well and clearly written, but also because it opens up the vast field of medical knowledge in a simple, interesting and engaging manner.

**Klinische elektrokardiographie, mit einem Grundriss der Arrhythmien**  
Von Dr. Wilhelm Dressler, Assistent der Herzstation in Wien. Mit einem Geleitwort von Prof. Dr. C. J. Rothberger. Second improved edition. Paper. Price, 12 marks. Pp 148, with 118 illustrations. Berlin Urban & Schwarzenberg, 1932.

In the preface to this work, Professor Rothberger expresses the belief that Dr. Dressler has met the requirements for introducing clinical electrocardiography to the practitioner of medicine. This belief is amply justified by the work. It is accurate, succinct, clear and a model of simplicity. It deals mainly with proved facts and touches only lightly that speculative field that brings confusion to all except the advanced student.

The first three chapters deal with the principles of the galvanometer, with the instrument itself and with the normal electrocardiogram. Following this is a



discussion of the alterations produced by malposition and by hypertrophy of the heart. Against this portion of the book a just criticism may be advanced. The author states, without qualification, that right or left ventricular hypertrophy may be determined from the electrocardiogram. Many observers believe that muscle mass and electrical activity are frequently but not always associated. It is probable that many normal hearts will show the curve of right or left ventricular preponderance.

The fifth chapter, which occupies the major portion of the book, has to do with the disorders of the heart beat. These are divided into two groups: disorders of stimulus production and those of stimulus conduction. In the first group are found sinus tachycardia and bradycardia, sinus arrhythmia, escaped beats, nodal rhythm, extrasystoles (auricular, nodal and ventricular), paroxysmal tachycardia (auricular, nodal and ventricular), parasystole, flutter and fibrillation. In the second group one finds auriculoventricular block, sino-auricular block, bundle branch block and arborization block.

The sixth and concluding chapter is a brief one which discusses the curves that indicate probable myocardial damage and coronary disease.

An especially pleasing feature of the book is the excellent summary that follows each group of tracings and sets forth the clinical recognition, the significance, the prognostic value and the therapeutic indications for the particular group.

Because of its simplicity and clarity, the book recommends itself equally to the undergraduate student and to the practitioner.

**The Chemistry of Tuberculosis.** By H. Gideon Wells and Esmond R. Long. Second edition. Cloth. Price, \$7. Pp. 500. Baltimore: Williams & Wilkins Company, 1932.

It may seem paradoxical that in a disease process seemingly so well defined and meticulously studied through these many decades as tuberculosis, a review such as that of Wells and Long would present a picture of absolute fluidity, of constantly changing views.

While paradoxical, it is nevertheless extremely hopeful. The tremendous activity in tuberculosis research which necessitates such constant revision is particularly apparent when one compares the second with the first edition of the review under consideration, and we may take considerable pride in the fact that American investigators have themselves contributed much to the newer information that is summarized in the book of Wells and Long.

Particularly the first chapters have been subjected to thorough revision so that they present a most complete review of the knowledge that has developed. There is no material expansion in the length of this portion of the book, because obsolete material has been largely eliminated. Some of the chapters have been practically rewritten, as, for instance, those on the chemistry of the tubercle bacillus and on the specific products of the tubercle bacillus. As a matter of fact, Long himself has contributed in a large measure to the advance that can here be recorded.

The material that deals with the chemical make-up of the patient has perhaps required less treatment. It is interesting to note the conservative tone in the discussion of chemotherapy. As one specific after another has been discarded, investigators have become more and more skeptical until today other paths, some of them older, are being assiduously retraced. Ultimately, too, we shall probably place much less reliance on the guinea-pig and study the patient more closely.

The first edition, from the time of its publication, has been on the desk of every tuberculosis worker. It filled a distinct need in making available in short, concise form a review of almost everything that had to be known about the chemistry of tuberculosis. The new edition will therefore be welcomed, as it is not only complete and clear, but accurate and fair in its evaluation of investigative work dealing with the tuberculosis problem.

Dr. Lydia DeWitt shared in the preparation of the first edition. As a result of her death, the revision of the third section has been in the hands of the two senior authors and all the newer methods of treatment have been reviewed by them.

## AN APPRECIATION

Dr Thayer was a member of the first Editorial Board of the ARCHIVES OF INTERNAL MEDICINE and continued to serve in this capacity for twenty-four years

His fine ideals and broad scholarship made him an invaluable member, and he played an important part in the endeavor to establish and maintain high standards. He never lost sight of the purpose for which the ARCHIVES was established namely, to further clinical investigation by supplying a medium of publication



WILLIAM SYDNEY THAYER, M D

In passing on manuscripts, he always bore in mind both the writer and the prospective reader. If a paper was not quite up to standard but showed evidence of industry and ideals, he would in his kindly manner suggest to the author certain modifications which would make the manuscript acceptable. His kindness to young physicians who showed promise of future attainments was unbounded.

In Dr Thayer's death, American medicine has lost one of its most cultured and scholarly members.

J L M



## SIMMONDS' DISEASE (CACHEXIA HYPOPHYSEOPRIVA)

REPORT OF A CASE WITH POSTMORTEM OBSERVATIONS AND A  
REVIEW OF THE LITERATURE

SOLOMON SILVER, M D

NEW YORK

Simmonds' disease may be defined as a clinical state, most common in women, characterized by progressive, extreme emaciation, premature aging, wrinkling of the facial skin, loss of pubic and axillary hair, dental caries and loss of libido and sexual function, accompanied by a depression of the basal metabolic rate. Untreated, it is a progressively fatal disease, usually terminating suddenly with a short period of coma. There are often mental disturbances closely simulating Kotsakoff's syndrome, so that the patients are sometimes first seen by the psychiatrist. The pathologic basis for the condition is varied. In general, it may be said that any process that destroys the anterior lobe of the pituitary gland may give rise to the clinical picture. A "splanchnomicia," an abnormal smallness of the viscera, is the only constant postmortem observation aside from changes in the pituitary body. This was first pointed out by Simmonds.<sup>1</sup>

Some idea of the various concepts of the fundamental nature of the disease can be obtained from the names that have been applied to it by different authors. Simmonds<sup>1</sup> called it "cachexia with fatal termination." Lichtwitz,<sup>2</sup> who did not believe that cachexia was an essential part of the clinical picture, called it Simmonds' disease. Colden<sup>3</sup> would name it "dystrophia cachecto genitalis" to indicate its relation to the syndrome of Frohlich, apparently unaware that Zondek<sup>4</sup> had already

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From the Medical Service, Mount Sinai Hospital

The case to be reported was observed in 1929, and the manuscript was prepared in 1930. Publication was unavoidably delayed until this time.

1 Simmonds, M. *Deutsche med. Wchnschr.* **40**: 322, 1914.

2 Lichtwitz, L. *Klin. Wchnschr.* **1**: 1877, 1922.

3 Colden, C. *Monatsbl. f. Augenh.* **82**: 769, 1929.

4 Zondek, H. *Ztschr. f. klin. Med.* **99**: 147, 1924.

used that term Urechia<sup>5</sup> suggested "cachexie tuberienne" to show that the region of the tuber cinereum, rather than the hypophysis, is primarily involved. Finally, Bauer<sup>6</sup> combined all the prevailing notions in the term "hypophysare-nervose kachexie."

It is obvious that the clinical picture existed before 1914, when it was first described by Simmonds. However, it does not seem that any of the earlier writers, Wagner,<sup>7</sup> Formanek,<sup>8</sup> Marburg<sup>9</sup> or Falta,<sup>10</sup> realized that a distinct clinical picture was associated with atrophy of the pituitary gland and was secondary to this pituitary change. Virchow,<sup>11</sup> who saw a case of pituitary gumma, did not record any typical findings. Goetsch,<sup>12</sup> in 1914, did not describe a clinical state associated with pituitary atrophy.

The disease has been almost completely ignored in the American literature. It is not even mentioned in the reviews of Abrahamson,<sup>13</sup> Englebach,<sup>14</sup> Tierney,<sup>15</sup> Frazier,<sup>16</sup> Eidelsberg<sup>17</sup> or Rowe and Lawrence.<sup>18</sup> The latter, with an unusually large series of over four hundred selected pituitary cases, did not record one of cachexia. They stated, "under weight was found chiefly in adolescents showing the Levi-Lorain type of disturbance and seldom amounted to more than 20%, the maximum recorded being 30%." The report of Good and Newman<sup>19</sup> is the only case recorded in the English literature.

There is no doubt that destruction of the parenchyma of the anterior lobe of the pituitary gland may produce the clinical picture that goes by the name of Simmonds' disease. It is my plan to review the recorded cases, add a case of my own and to indicate the basis on which the condition may be recognized *intra vitam*.

5 Urechia, C. J., and Elekes, N. *Encephale* **21** 352, 1925.

6 Bauer, Julius. *Innere Sekretion*, Berlin, Julius Springer, 1927.

7 Wagner. *Arch f. Heilkund* **3** 381, 1862 (not seen in original).

8 Formanek, F. *Wien klin. Wchnschr.* **22** 603, 1909.

9 Marburg. *Ztschr. f. Nervenhe.* **36** 116, 1909.

10 Falta, Wilhelm. *Die Erkrankungen der Blutdrüsen*, Berlin, Julius Springer, 1913.

11 Virchow. *Virchows Arch. f. path. Anat.* **15** 299, 1858.

12 Goetsch, E. *Quart. J. Med.* **7** 173, 1914.

13 Abrahamson, Isador, and Cleimenko, Hyman. *A Study of One Hundred Selected Cases of Pituitary Disease*, *J. A. M. A.* **69** 281 (July 28) 1917.

14 Englebach, W. *Endocrinology* **4** 347, 1920.

15 Tierney, J. L. *Endocrinology* **7** 536, 1923.

16 Frazier, C. H., and Grant, F. C. *Pituitary Disorder*, *J. A. M. A.* **85** 1103 (Oct. 10) 1925.

17 Eidelsberg, Joseph. *Hypopituitarism*, *J. A. M. A.* **89** 449 (Aug. 6) 1927.

18 Rowe, A. W., and Lawrence, C. H. *Endocrinology* **12** 245, 1928.

19 Good, T. S., and Newman, K. O. *Lancet* **1** 765 (April 13) 1929.

Credit for the first clinical diagnosis of pituitary cachexia belongs to Nonne,<sup>20</sup> who, knowing of Simmonds' reports, recognized a case in 1919. The diagnosis in this case was later confirmed by Simmonds at autopsy.

#### REPORT OF A CASE

*Clinical History*—A Hungarian housewife, aged 53, had lived in New York for the past thirty-seven years. Her father and mother had died at advanced ages of unknown causes. She knew of no illness resembling her own that had occurred in her family. In her infancy she suffered from an attack of "smallpox." Her menses began at 14 and were regular until the onset of her present illness. She married at 20 and was pregnant eight times. Three children were well, two died



Figure 1



Figure 2

Fig. 1—The patient at 18 years of age

Fig. 2—The patient at 30 years, emaciation is just indicated

in infancy, and three pregnancies terminated in abortions. No information regarding the nature of the deliveries could be obtained.

At 40, shortly after the birth of her last child, the patient's menses ceased. She noticed that she tired easily and could no longer do her usual household work. At that time she weighed 130 pounds (59 Kg) and showed no evidences of any illness.

For the last twelve years of her life she had become progressively weaker and more cachectic. This change had been most accentuated in the past eighteen months. At the time of examination the patient weighed only 60 pounds (27.2 Kg),

20 Nonne and Bostroem. *Deutsche med. Wchnschr.* 44: 871, 1919.

a loss of 53 per cent of her former body weight. Her teeth had become carious, and most of them had fallen out. Menses and libido had been absent since her fortieth year. Emaciation had been progressive and marked, and it was believed that the patient was suffering from a latent carcinoma.

Three weeks before admission she suffered from an attack of abdominal cramps and diarrhea which yielded to the usual therapy. Blood was never noted in the stool. This diarrhea had not returned, but the patient had a moderate anorexia.

*Examination*—Physical examination revealed an extremely cachectic woman who had lost practically all her subcutaneous fat. The cachexia was as extreme as one sees in the most advanced cases of carcinomatosis or tuberculosis. Literally, the patient presented "nothing but skin and bones." The skin was of a sallow, yellow hue, but there was no icterus. The facial skin was wrinkled. The eye-

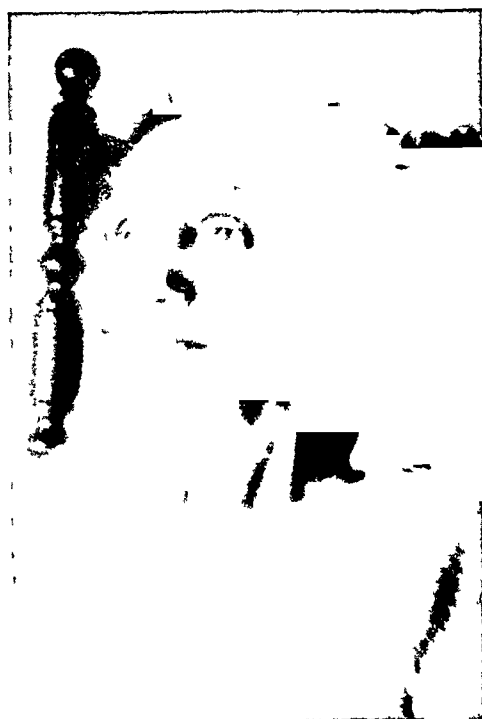


Fig 3—The patient at 51, cachexia is obvious

brows were sparse, especially at the outer margin. The eyes were sunken and the conjunctivae pale. The fundus showed atherosclerotic vessels, but no other changes. The patient was almost edentulous, and the few remaining teeth were very carious. There was no pigmentation of the mucous membranes. The thyroid could not be felt. The breasts were very atrophic. No abnormal findings were noted in the thorax. No abdominal viscera could be felt through the extremely thin abdominal wall. The wasting was very marked in the extremities, and there was a slight grade of pretibial edema (nutritional?). There were no positive neurologic findings. The pubic hair was very sparse, as was the hair in the axillae. The genitalia were atrophic.

The blood pressure was 120 systolic and 80 diastolic, the hemoglobin, 47 per cent, and the color index, 0.9. The leukocytes numbered 6,400, of which 60 per cent were polymorphonuclears, 30 per cent lymphocytes, 7 per cent monocytes, 1 per cent myelocytes, and 1 per cent lymphoblasts. The von Pirquet test gave

negative results. The stool was normal and contained no blood. A gastric test meal revealed complete achlorhydria even after 0.5 mg of histamine subcutaneously, but ferments were present. There was no polyuria, and the specific gravity averaged 1.016. The urine was normal. The blood sugar was 90 mg per hundred cubic centimeters, and the urea nitrogen, 14 mg. The basal metabolic rate was minus 10 per cent. X-ray pictures of the sella turcica, stomach and chest revealed no abnormalities.

Although the case had been referred with the suggestion that the patient was suffering from an intra-abdominal neoplasm, at no time was the admission diagnosis of cachexia of hypophyseal origin doubted. The extreme emaciation, repeated pregnancies, early loss of menses, sallow, wrinkled skin, genital atrophy and loss of pubic and axillary hair gave indications that the cachexia was not of the usual variety. The patient died suddenly several days after admission.



Fig. 4—One week before death, cachexia is extreme.

*Pathologic Data*—Autopsy was performed twenty-four hours after death. The body was that of an elderly woman, extremely undernourished. There was no jaundice. There was some edema of the legs.

The panniculus adiposus was entirely absent. There was a small amount of ascites. The peritoneal surfaces of the abdomen were everywhere smooth and normal.

The heart was very small, weighing only 170 Gm. The pericardium was normal. The valves and chambers were normal. The coronary arteries were tortuous and showed moderate sclerosis. The aorta was normal.

There was moderate bilateral emphysema. The upper portion of the lower lobe of the right lung showed a calcified primary infection situated subpleurally. The right lung weighed 425 Gm, and the left lung, 340 Gm. There was a moderate grade of pulmonary edema.



The liver weighed 895 Gm. The capsule was smooth. On cut section, the architecture of the liver was poorly visualized. The gallbladder and ducts were normal.

The spleen weighed only 70 Gm, otherwise, it was normal.

The kidneys were small and firm and weighed 100 Gm each. The capsule stripped with difficulty, numerous gray areas about 0.5 by 0.25 cm in the rough surface being uncovered. The cortex and medulla were injected. The pelvis, ureters and bladder were normal.

There was some slight ulcerations in the lower third of the esophagus. There was an hour-glass constriction in the distal third of the stomach, which showed no ulcerations. In the small intestine there were numerous superficial small ulcera-

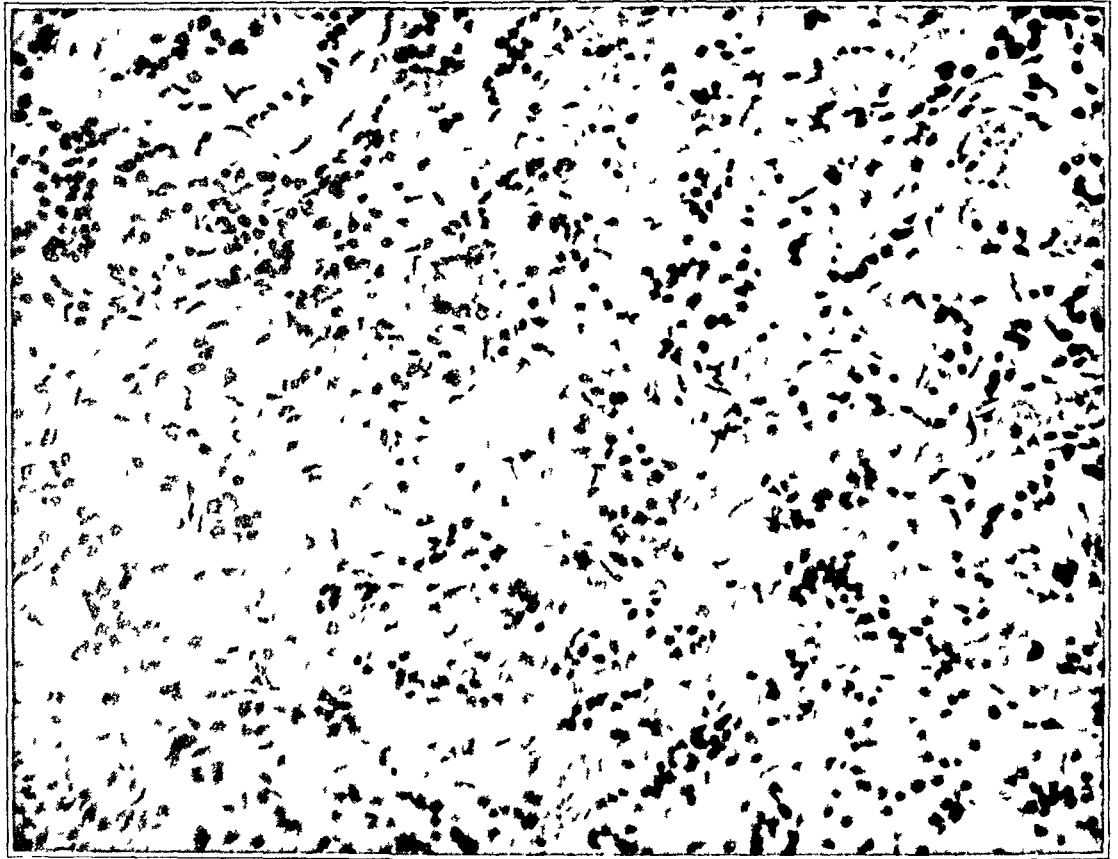


Fig 5—Section of the anterior lobe of the pituitary, showing the marked increase in interstitial tissue and the reduction in parenchyma.

tions, some as large as a small pea. No evidences of these ulcers could be seen on the serosa. The large intestine was normal.

The uterus was senile. The ovaries were small.

The pancreas weighed 70 Gm.

The suprarenal glands weighed 15 Gm each. The cortex was very thin.

The thyroid was normal on section.

*Microscopic Data*—There was marked atrophy of the heart, with pigmentation.

Peripheral fatty infiltration of the liver was present. The cells about the central vein showed a great amount of pigment. Brown atrophy was present.

There were small areas of fibrosis and moderate arteriosclerosis of the kidneys.

Atrophy of the acini of the pancreas was evident

The thyroid was atrophied

There was atrophy of the medulla of the suprarenals

There were superficial ulcerations of the mucosa of the intestines, with an inflammatory reaction

*Conclusions* (Dr Klemperer) —“A case of extreme cachexia in a woman of 53 years Autopsy and examination of the internal organs did not reveal anything but an extreme atrophy The glands of internal secretion were not involved in any *sclerotic* process The only positive findings were the marked hyperplastic

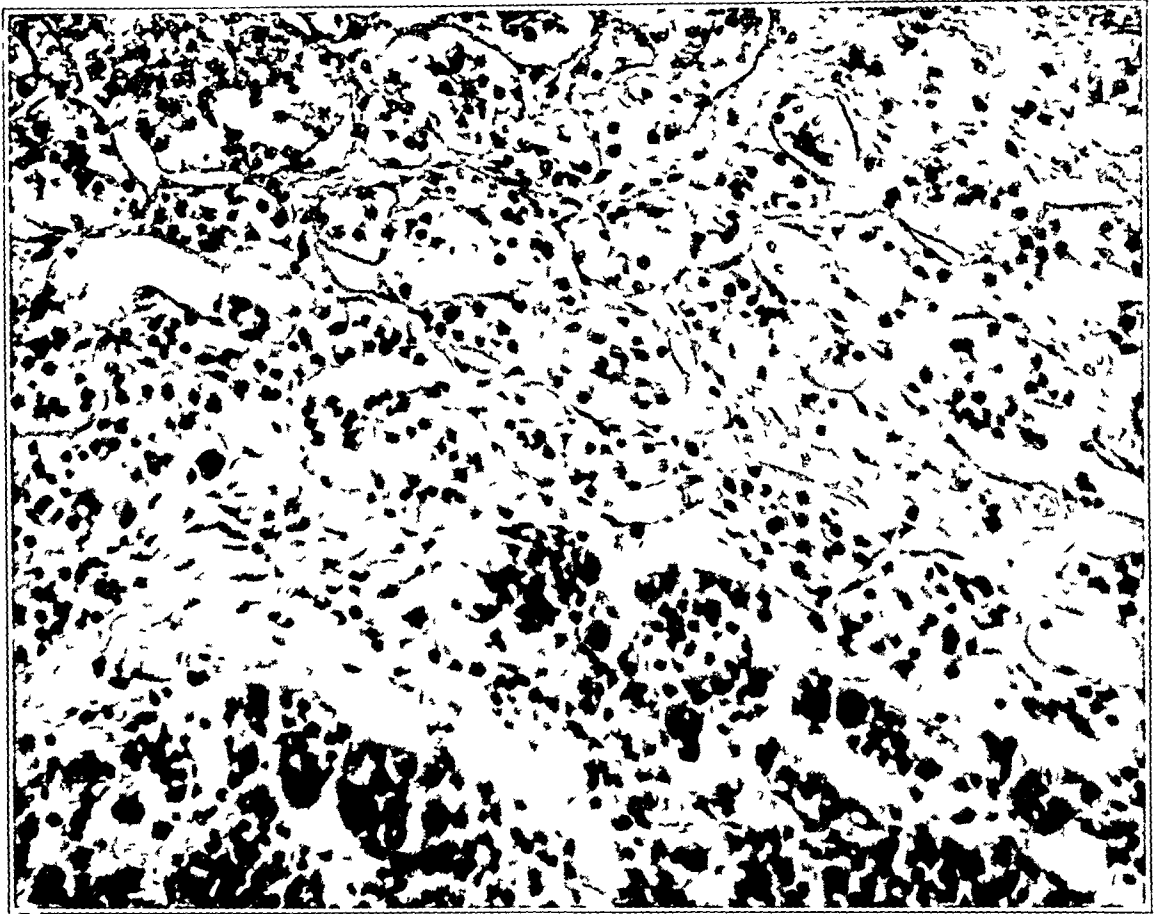


Fig 6—Section of the anterior lobe of the pituitary, showing advanced disintegration of the parenchyma

gastritis and the superficial catarrhal ulcers of the small intestines From these findings an explanation as to the cause of the cachexia cannot be given”

The brain was examined by Dr J H Globus, and the following is his report of the positive findings “The pituitary body was smaller than normal Microscopically it showed marked alterations in its anterior lobe There was extensive fibrosis and marked reduction in the parenchymatous elements The latter showed advanced degeneration as evidenced by shrinkage and desquamation of cells and pyknosis of the nuclei

“The histologic appearance of this organ was in full accord with that described in Simmonds' disease

“The hypothalamic region revealed no definite pathologic alteration”

## SUMMARY OF REPORTED CASES

At this point I wish to add a few notes regarding cases that either have been published as Simmonds' disease or have been quoted by writers other than the original authors as such. They are added for the sake of completeness with a word of criticism.

The case of Josephy<sup>21</sup> is not to be considered as one of Simmonds' disease because the clinical picture is insufficient and the loss of weight occurred just ante mortem.

The case of Hirsch<sup>22</sup> has been quoted as one of pituitary cachexia, but as the patient had a carcinoma of the esophagus with extensive metastases, one need not implicate the pituitary in the causation of the cachexia, although the gland showed some changes.

The case of Knoll<sup>23</sup> cannot be accepted as a proved case. There was no cachexia, and the postmortem examination was limited to the head. There is every reason to believe that the patient suffered from a full blown, active, milary tuberculosis and that the destruction of the pituitary was only one manifestation of this generalized process.

The case of Lindemann<sup>24</sup> has been quoted as a case of Simmonds' disease, although the author expressly favored a diagnosis of pluriglandular sclerosis. In addition, there was no cachexia, and there seems to be no reason to include the case with those of pituitary disease.

The second case of Jakob<sup>25</sup> can scarcely be recognized as a case of Simmonds' disease because there was a fresh tuberculous meningitis. However, the hypothermia, bradycardia, achylia, mental changes and loss of pubic and axillary hair suggest some pituitary disturbance.

The case of Worms and Delater<sup>26</sup> cannot be accepted as a report of Simmonds' disease, although it has been so presented by others. The authors state distinctly that no pituitary symptoms were present and that the testes were normal. This case is best considered as one of the group that shows no characteristic clinical picture in spite of complete pituitary destruction.

The interesting case of Pribram<sup>27</sup> is difficult to classify exactly. At 31 the patient had a difficult labor after which she "aged 20 years in two weeks." Later she lost all her teeth, became amenorrheic, lost her eyebrows, axillary and pubic hair and suffered from a complete loss of libido. The patient had episodes of "hibernation" from which she could be aroused by thyroid extract. She died at 50 years of age. Postmortem

21 Josephy, H. *Ztschr f d ges Neurol u Psychiat* **58** 56, 1920.

22 Hirsch, O. *Deutsches Arch f klin Med* **140** 323, 1920.

23 Knoll, W. *Wien Arch f inn Med* **4** 555, 1922.

24 Lindemann. *Virchows Arch f path Anat* **240** 11, 1923.

25 Jakob, A. *Virchows Arch f path Anat* **246** 151, 1923.

26 Worms, G., and Delater, G. *Rev neurol* **2** 361, 1925.

27 Pribram, B. O. *Virchows Arch f path Anat* **264** 498, 1927.

examination revealed an advanced hypophysitis and thyroiditis of unclear etiology, probably secondary to some form of sepsis. It seems likely that many of the symptoms were due to an insufficiency of the anterior pituitary lobe. This is apparently the same case that Pribram reported in 1922 and is abstracted here as case 12 (table 1).

The case of Van Bogaert<sup>28</sup> cannot be considered one of Simmonds' disease. The patient suffered from dystrophia adiposogenitalis (Frohlich) and lost weight only terminally. In addition, the anterior pituitary lobe was quite normal. In this case the tumor was suprasellar, and it is interesting to note that hypothermia and a lowered basal metabolic rate were present possibly as indications of symptoms in the midbrain secondary to the primary focus.

The case of Frazier<sup>29</sup> cannot be accepted. The patient was a boy, the clinical picture was not definite, and a complicating syphilis was probably present. In addition, a postmortem examination was not performed and for reasons noted this alone would exclude the case.

The following four authors have presented cases without anatomic confirmation as Simmonds' disease. None of them, however, seems to have a case that is to be accepted without doubt.

It does not seem to me that Lichtwitz has enough evidence to consider the three cases that he presents as clinically likely examples of Simmonds' disease.

Although Schneider<sup>30</sup> considered the cachexia in his case of hypophyseal origin, it seems best to attribute the lack of development and stigmas of infantilism to the extensive tuberculosis from which the patient suffered rather than to a primary pituitary lesion.

The case of Korovnikov and Beresniak<sup>31</sup> does not seem to have enough features of Simmonds' disease to warrant including it as a likely case.

One can scarcely accept the case of de Rudder<sup>32</sup>. In spite of the depression of the basal metabolic rate and extreme cachexia (the 9 year old patient presented the weight of a 1½ year old infant), there are not enough characteristics to be certain that a marked abiotrophy of the central nervous system was not present rather than a specific hypophyseal disorder.

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28 Van Bogaert, Ludo. The Thalamic and Parkinsonian Types of Infundibular Tumors, *Arch Neurol & Psychiat* **19** 377 (March) 1928.

29 Frazier, C. H. Pituitary Cachexia, *Arch Neurol & Psychiat* **21** 1 (Jan) 1929.

30 Schneider. *Wien klin Wchnschr* **35** 233, 1922.

31 Korovnikov, A., and Beresniak, M. E. *Klin med* **6** 539, 1928.

32 de Rudder, B. *Ztschr f Kinderh* **50** 113, 1930.

TABLE 1—Cases Confirmed by Postmortem Examination, Symptomatology and Physical Findings

Case	Author	Sex	Age	Type of Onset	Duration in Years	Cachexia	Asthenia	Premature Aging	Age at Menopause	Number of Pregnancies	Genital Atrophy (Male)	Loss of Libido	Loss of Pubic Hair	Loss of Vaginal Hair	Atrophy of Jaw	Loss of Teeth	Hypotension	Hypothermia	Leukopenia, per Cent	Anemia	Additional Findings
1	Simmonds <sup>1</sup>	F	46	Unknown	Unknown	+	+	+	22	11	+	+	+	+	+	+	+	+	24	5	Bradycardia 60% Polyuria
2	Marsch <sup>24</sup>	F	33	After birth of twins	11	+	+	+	22	11	+	+	+	+	+	+	+	+	24	5	Bradycardia 60% Polyuria
3	Simmonds <sup>33a</sup>	M	58	Gradual with asthenia	2	+	+	+	22	11	+	+	+	+	+	+	+	+	24	5	Bradycardia 60% Polyuria
4	Simmonds <sup>33a</sup>	F	9	Gradual with asthenia	1	+	+	+	22	11	+	+	+	+	+	+	+	+	24	5	Bradycardia 60% Polyuria
5	Frankel, E. Deutsche med. Wchnschr. <sup>43</sup>	F	45	After pregnancy	9	+	+	+	22	11	+	+	+	+	+	+	+	+	24	5	Bradycardia 60% Polyuria
6	1369, 1916, Neurol Centralbl. <sup>35</sup>	F	27	Gradual with asthenia	1	+	+	+	22	11	+	+	+	+	+	+	+	+	24	5	Bradycardia 60% Polyuria
7	Schlagenhafer <sup>22</sup>	F	48	After pregnancy	18	+	+	+	22	11	+	+	+	+	+	+	+	+	24	5	Bradycardia 60% Polyuria
8	Simmonds <sup>33b</sup>	F	35	No history	known	+	+	+	22	11	+	+	+	+	+	+	+	+	24	5	Bradycardia 60% Polyuria
9	Frhr. <sup>38</sup> Reiche <sup>41</sup>	F	50	Became weak after febrile illness at 21	26	+	+	+	22	11	+	+	+	+	+	+	+	+	24	5	Bradycardia 60% Polyuria
10	Schaefer <sup>57</sup>	F	22	After rheumatic fever at 21	1	+	+	+	22	11	+	+	+	+	+	+	+	+	24	5	Bradycardia 60% Polyuria
11	Budde, M. Frankfurt Ztschr. f. Path.	F	27	Gradual	+	+	+	+	22	11	+	+	+	+	+	+	+	+	24	5	Bradycardia 60% Polyuria
12	Pribram, B. O. Verh. d. deutsch. Kong. f. inn. Med.	F	32	Sudden after manual removal of placenta	+	+	+	+	22	11	+	+	+	+	+	+	+	+	24	5	Bradycardia 60% Polyuria
13	von Monakow <sup>64</sup>	M	60	Gradual	7 mo	+	+	+	22	11	+	+	+	+	+	+	+	+	24	5	Bradycardia 60% Polyuria
14	Jaffe <sup>58</sup>	M	33	Gradual	8	+	+	+	22	11	+	+	+	+	+	+	+	+	24	5	Bradycardia 60% Polyuria
15	Simons <sup>35</sup>	F	42	Gradual	+	+	+	+	22	11	+	+	+	+	+	+	+	+	24	5	Bradycardia 60% Polyuria
16	Kelmann <sup>37</sup>	F	20	After puerperal signs	1	+	+	+	22	11	+	+	+	+	+	+	+	+	24	5	Bradycardia 60% Polyuria
17	Hochstetter and Vat <sup>66</sup>	M	34	Gradual with headache and loss of libido	1	+	+	+	22	11	+	+	+	+	+	+	+	+	24	5	Bradycardia 60% Polyuria
18	Colden <sup>3</sup>	M	44	With psychosis called Korsakoff	+	+	+	+	22	11	+	+	+	+	+	+	+	+	24	5	Bradycardia 60% Polyuria
19	Grabe <sup>40</sup>	F	40	Sudden after pregnancy	3	+	+	+	22	11	+	+	+	+	+	+	+	+	24	5	Bradycardia 60% Polyuria
20	Jakob, A. Deutsche med. Wchnschr. <sup>49</sup>	F	10	After pregnancy	5	+	+	+	22	11	+	+	+	+	+	+	+	+	24	5	Bradycardia 60% Polyuria

[illegible]

TABLE 3—Clinical Cases, Symptomatology and Physical Findings<sup>1</sup>

Case	Author	Age	Type of Onset	Duration in Years	Cachexia	Asthenia	Premature Aging	Age at Menopause	Number of Pregnancies	Genital Atrophy (Male)	Loss of Libido	Loss of Pubic Hair	Loss of Axillary Hair	Atrophy of Jaw	Loss of Teeth	Hypotension	Hypothermia	Eosinophilia, per Cent	Anemia	Additional Findings
1	Simmonds <sup>1</sup>	46	After puerperal sepsis	10	+	+	+	+	5											No eyebrows, improved on antisyphilitic therapy
2	Cyran <sup>51</sup>	48	After fracture of skull	In definite	+	+	+											10		Improved on antisyphilitic therapy
3	Reye Med Klin 16, 1313, 1920	50	Gradual	3½	+	+	+		11	+										No eyebrows, improved on antisyphilitic therapy
4	Felt, H. Med Klin 16, 421, 1920	53	Gradual	In definite	+	+	+													Improved on antisyphilitic therapy
5	Buchler, P. Ztschr f d ges Neurol u Psychiat 72, 207, 1921	29	Gradual with loss of weight	7	+	+		+22										8		No eyebrows, improved on syphilitic and pituitary extract, menses returned
6	Reye Deutsche med Wchnschr 54, 606, 1923, footnote 36	45	After puerperal sepsis	17	+	+	+	28	6											Basal metabolic rate, -49%
7	Zondek <sup>43</sup>	42	With amenorrhea	8	+	+	+	+31		+										Basal metabolic rate, 69 cc of oxygen per minute
8	Plaut <sup>44</sup>	54	Gradual	15	+	+	+													Basal metabolic rate, -3%
9	von Gerloczy <sup>48</sup>	18	After roentgen treatment of pituitary	1	+	+	+													
10	Szondy Klin Wchnschr 2, 902, 1923	49	No details																	
11	Reye <sup>36</sup>	31	After delivery with hemorrhage	6	+	+	+	+27	6	+	+									No eyebrows, basal metabolic rate, -31%, improved with pituitary therapy
12	Reye <sup>36</sup>	36	After birth of twins	3	+	+	+	+33		+	+							12		No eyebrows, cured by antisyphilitic therapy
13	Bauer <sup>6</sup>	22	Gradual	In definite	Mod	+														Spontaneous development of Simmonds' disease in pituitary dwarf
14	Sucher, W. Mun chen med Wchnschr 74, 1795, 1927	21	After manual removal of placenta		Mod	+	+				+									Improved on pituitary extract
15	di Guglielmo, G Bull d med chir di betes insipidus	29	After syphilis and diabetes insipidus	3	+	+	+	+26												Improved on pituitary extract
16	Pavia <sup>2</sup> 167, 1927	53	Loss of weight	1	+															Improved on pituitary extract
17	Herman, K Klin Wchnschr 7, 944, 1928, Rev franc d'endocrinol 301, 1928	35	After complicated labor	3	+	+	+	12	3		+									Improved on pituitary extract
18	Golden <sup>3</sup>	29	Signs of pituitary tumor	+	+		+	120												
19	Riese <sup>71</sup>	10	Gradual with weakness	1	+	+	+	+	6		+									No eyelashes or eyebrows

\* Although I believe that no case of Simmonds' disease can be accepted as definitely proved unless the clinical impression has been confirmed by a complete postmortem examination, yet I feel that the diagnosis can be made intra vitam with a high degree of accuracy. It is my plan to review briefly in this table the essential features of those cases that have been reported in the literature in which the diagnosis has not been submitted to autopsy confirmation, but in which the evidence seems convincing that the lesion lay in the anterior lobe of the hypophysis.

However, one should expect to find considerable emaciation. The greatest loss of weight recorded is in the case of Simons,<sup>35</sup> whose patient lost 51 Kg, or 63 per cent of her body weight. Losses of 40, 50 and 60 pounds (18.1, 22.7 and 27.2 Kg) are not unusual. The distribution of the loss of weight is not constant and shows no characteristics valuable in the diagnosis.

Reye<sup>36</sup> has insisted that the clinical diagnosis can be made in the precachectic stage. He says that the patients have a slightly yellowish skin, resembling that seen in nephritis or pernicious anemia, and give one the impression of having a slight grade of myxedema. However, they are not helped by the administration of thyroid.

The patients present a fairly characteristic appearance. They are prematurely aged, the skin of the face is wrinkled, and this, combined with the loss of teeth and atrophy of the lower jaw, gives them a typical aged look. Another outstanding feature is the recession of the secondary skin characteristics. Women become amenorrheic, and there is usually a complete loss of libido. Complete amenorrhea at the age of 16 has been reported by Keilmann<sup>37</sup> and at 24 by Fahr<sup>38</sup> and Reiche.<sup>39</sup> The external genitalia, uterus and ovaries become atrophic. In men there is testicular atrophy with loss of libido and potency. The prostate and seminal vesicles undergo atrophic changes. The pubic and axillary hair becomes scant or falls out completely. The beard and moustache of men become sparse. Loss of eyebrows and eyelashes has been noted by many writers. There is usually a severe disturbance of dentition. It is interesting that the teeth are often lost without evidence of an advanced caries.

The patients are usually apathetic and easily exhausted. Dizziness, fainting and periods of unconsciousness are not uncommon. Convulsions are rare, but have been recorded. Mental disturbances are marked and may be the dominant clinical feature. The patients may be disoriented and require restraint. They have been observed on psychopathic pavilions as presenting cases of Korsakoff's syndrome.

Headache is a common complaint. There is no characteristic "pituitary headache" so far as the analysis of the cases allows. Vomiting is commonly associated with the headache even when no intracranial tumor is present.

Hypothermia is a quite constant finding, although there are case reports of a low grade fever. The temperature may range between

35 Simons *Zentralbl f d ges Neurol u Psychiat* **30** 125, 1922, **39** 191, 1925

36 Reye *Munchen med Wchnschr* **73** 902, 1926

37 Keilmann *Centralbl f allg Path u path Anat* **32** 113, 1922

38 Fahr, T *Deutsche med Wchnschr* **44** 206, 1918

39 Reiche, F *Med Klin* **14** 984, 1918



35 and 36 C (95 and 96.8 F) for months. Readings as low as 34 C (93.2 F) have been recorded by Grabe<sup>40</sup>

The fundus oculi yields useful localizing information if there is an expanding intracranial lesion. As in other diseases of the pituitary region, the visual fields should be studied for color as well as for form.

The blood pressure is always low, and there is usually a bradycardia. Anemia is a constant finding, and the hemoglobin averages 50 per cent. The color index is usually less than 1. The leukocytes are often reduced in number. An eosinophilia,<sup>41</sup> which may reach 22 per cent, is an interesting and common finding. Hypoglycemia, as well as hyperchloremia, has been noted.

Roentgenograms should always be taken of the sella turcica. Evidences of a destructive, expanding lesion may be found, or one may find an unusually small sella. Lichtwitz<sup>2</sup> pointed out that cases of Simmonds' disease showed calcification in the pituitary region on roentgenograms. However, he had no postmortem controls, and later Reiche<sup>42</sup> was able to show that these shadows were not in the pituitary body but merely on the dura.

It is difficult to demonstrate the microsplanchnia during life, but the percussion outlines of the liver, heart and spleen, as well as the size of the heart, should be determined by roentgenograms.

Following the observation of Zondek,<sup>43</sup> the determination of the basal metabolic rate in Simmonds' disease has become important. It is always depressed. Records of minus 49 per cent have been obtained by Reye,<sup>36</sup> findings which are lower than those in complete myxedema. The specific dynamic action of a protein test meal should be determined. According to Plaut<sup>44</sup> and Kestner, Liebeschütz-Plaut and Schadow,<sup>45</sup> the increase in the oxygen consumption that usually follows a protein meal is either absent or much diminished in pituitary cachexia.

As Zondek<sup>46a</sup> pointed out, the ability of these patients to excrete water and salt is often embarrassed. One liter of water or 10 Gm of sodium chloride is given and the excretion studied. Normally, the water should be excreted in four hours and the salt in twenty-four. In Simmonds' disease, there is usually a marked retention of both water and salt.

40 Grabe. *Deutsche med. Wchnschr.* **49** 735, 1923.

41 Reiche<sup>39</sup>. *Fahr* <sup>38</sup>

42 Reiche, F. *Med. Klin.* **23** 1569, 1927.

43 Zondek, H. *Klin. Wchnschr.* **1** 1385, 1922.

44 Plaut, A. *Deutsches Arch. f. klin. Med.* **139** 285, 1922.

45 Kestner, O., Liebeschütz-Plaut, R., and Schadow, H. *Klin. Wchnschr.* **5** 1646, 1926.

46 (a) Zondek and Marx. *Deutsche med. Wchnschr.* **53** 598, 1927. (b) Jungmann, P. *Klin. Wchnschr.* **2** 18, 1923.

Achylia gastrica has been noted several times,<sup>39</sup> and was present in the case here reported

*Differential Diagnosis* —The diagnosis of pituitary cachexia depends, to a large extent, on the absence of any of the other, more common causes of extreme loss of weight. If one can discover another adequate explanation for the cachexia, the diagnosis of Simmonds' disease should be made only with extreme reserve. However, in the cachexias secondary to tuberculosis, carcinoma or other conditions one does not find the recession of the secondary sex characteristics that is so marked in Simmonds' disease. Cachexia with the loss of pubic and axillary hair, especially if combined with atrophic genitalia and gonads and loss of sexual power, should attract attention to the pituitary gland as a possible source of the syndrome. It is noted that the loss of hair in the axillae and on the pubis is uncommon in the usual cachexias. If the history indicates that the illness began after childbirth, especially if the labor was difficult and accompanied by hemorrhage or followed by sepsis, one should be on the alert for a case of hypophyseal cachexia.

All authors note that the disease must be differentiated from the pluriglandular insufficiency of Claude and Gougerot<sup>47</sup> or the pluriglandular sclerosis of Faltz.<sup>10</sup> At times this distinction may be impossible clinically, but the conditions can usually be separated. If one accepts pluriglandular sclerosis as a "simultaneous post inflammatory sclerosis of all the endocrine glands," one should expect symptoms referable to more than one gland. True cases of pluriglandular sclerosis, of which there are not many, show the skin and facies of myxedema as evidence of thyroid insufficiency. They may show the pigmentation of the skin and mucous membranes as well as the hypotension, hypoglycemia and adynamia that go with suprarenal failure. Tetany, latent or active, may reveal a parathyroid lesion, or glycosuria a sclerosis of the pancreas. Then, too, an etiologic factor for the disease may be found in syphilis or tuberculosis.

It is true clinically, and has been demonstrated pathologically many times, that destruction of the pituitary gives rise to secondary changes in the other glands. These alterations are most marked in the gonads, thyroid and suprarenals. However, these changes always follow the pituitary damage and are secondary to it, rather than simultaneous with it as is necessary in true pluriglandular sclerosis. Simmonds has shown that there can be extensive primary pituitary change with the other endocrine glands remaining normal.

Clinically, there are cases in which the pluriglandular involvement is so manifest that one cannot tell whether the glands were affected simultaneously or whether the changes in one produced the lesions in

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<sup>47</sup> Gougerot and Guy. *Nouv. Icono. de l' Salpêtrière* **24** 449, 1911. Claude and Gougerot. *Compt. rend. Soc. de biol.* **63** 785, 1907.

the other. In these cases only a careful, complete postmortem examination by a competent pathologist can determine the time relationship of the various lesions. However, although in some cases the clinical distinction between pluriglandular sclerosis and Simmonds' disease must await the pathologist's confirmation, in the majority of cases one can make the differential diagnosis clinically with a high degree of accuracy.

In separating cachexias of pituitary origin from others, the determination of the basal metabolic rate is often of great value. Depression of metabolism to levels lower than ever noted before has been reported in Simmonds' disease. This finding is of particular significance because in almost all other cachexias, especially those due to carcinoma and tuberculosis, the basal metabolic rate is usually elevated above the normal.

In short, one should suspect hypophyseal cachexia in every case of marked loss of weight. If careful clinical, roentgen and laboratory examinations reveal no other cause for the emaciation, one should be careful lest a case of Simmonds' disease be missed. The onset of symptoms after a complicated labor, loss of sexual function, falling out of axillary and pubic hair, loss of teeth, especially without caries, anemia with eosinophilia, hypotension, bradycardia, hypothermia, achylia gastrica, depression of the basal metabolic rate and loss of specific dynamic action of proteins are to be looked for. Of course, all these symptoms will not be found in any one case, but the presence of several of them is always suggestive.

If the observations of Reye,<sup>48</sup> Lichtwitz<sup>2</sup> and others are true, the improvement on treatment with anterior pituitary extract should be a valuable aid in the diagnosis.

#### PATHOLOGIC ANATOMY

If one accepts the premise that the anterior lobe of the pituitary gland has an irreplaceable function, then it is to be expected that destruction of this lobe will give rise to changes in the organism. I believe that the evidence is strong enough to accept the correlation of Simmonds' syndrome with a lesion destroying the anterior hypophysis. It follows that the symptoms should be fundamentally the same no matter what the nature of the process that results in the pituitary change. It has been shown that the recorded facts bear out these assumptions.

Simmonds<sup>49</sup> believed that most of the cases were due to infarction of the anterior lobe secondary to emboli. It was thought that embolic lesions of the pituitary were rare, but Simmonds was able to show that they were not uncommon and that the anterior lobe was more commonly

48 Reye. *Deutsche Ztschr f Nervenhe* **68** 153, 1921, footnote 36

49 Simmonds, M. *Virchows Arch f path Anat* **217** 226, 1914

affected than the posterior in the ratio of seven to four. He also demonstrated that embolism to the anterior lobe results in anemic infarction because the vessels are functionally end-arteries. Merkel<sup>50</sup> demonstrated the pituitary gland in a case of sepsis in which seven eighths of the anterior lobe was destroyed, while the posterior lobe remained intact. Baló,<sup>51</sup> who studied postpartum embolism of the pituitary gland, came to the conclusion that small emboli usually had no functional significance, that ones of medium size gave rise to the clinical picture of Simmonds' disease, but that, following large embolic lesions, the death of the patient resulted before the development of any changes recognizable clinically.

The observation of Schlagenhafer<sup>52</sup> that tuberculosis of the pituitary with destruction can give rise to Simmonds' disease was made in 1916. In 1918, Froboese<sup>53</sup> noted tuberculous (?) destruction of part of the pituitary gland.

The clinical observation of Cyran,<sup>54</sup> later confirmed pathologically by Reinhardt<sup>55</sup> and Shereshevsky,<sup>56</sup> showed that symptoms of pituitary insufficiency may follow fractures of the skull with hemorrhage about the midbrain.

In 1919, Schaefer<sup>57</sup> reported a case of pituitary destruction due either to syphilis or to tuberculosis in which the syndrome of Simmonds developed. Jaffe<sup>58</sup> and Buday<sup>59</sup> were able to add cases due to gummas of the hypophysis.

Tumors, primary and secondary, of the hypophysis with Simmonds' syndrome have been reported by Simmonds,<sup>33a</sup> Lang,<sup>60</sup> Honlinger and Stricker,<sup>61</sup> Pennetti,<sup>62</sup> Mogilnitzky<sup>63</sup> and Frazier.<sup>29</sup>

Postinflammatory destruction of undetermined origin has been reported by von Monakow<sup>64</sup> and Pribram.<sup>27</sup>

50 Merkel, H. *Verhandl d deutsch path Gesellsch* **17**:193, 1914

51 Baló, J. *Beitr z path Anat u z allg Path* **72** 599, 1923-1924

52 Schlagenhafer. *Virchows Arch f path Anat* **222** 249, 1916

53 Froboese, C. *Centralbl f allg Path u path. Anat* **29** 145, 1918

54 Cyran. *Deutsche med Wchnschr* **45** 1261, 1918

55 Reinhardt. *Klin Wchnschr* **1** 2309, 1922

56 Shereshevsky, N. A. *Vrách delo, Kkarhov* **8** 1093, 1925, *Centralbl f d ges Neurol* **42** 434, 1925

57 Schaefer. *Dissertation, Path Inst, Jena, 1919*, *Centralbl f allg Path u path Anat* **30** 520, 1920

58 Jaffe. *Frankfurt Ztschr f Path* **27** 324, 1922

59 Buday. *Klin Wchnschr* **2** 902, 1923

60 Lang, F. J. *Wien klin Wchnschr* **37** 977, 1924

61 Honlinger, H., and Stricker, W. *Frankfurt Ztschr f Path* **29** 492, 1923

62 Pennetti, G. *Riforma med* **44** 9, 1928

63 Mogilnitzky, B. N. *Virchows Arch f path Anat* **269** 1, 1928

64 von Monakow, P. *Verhandl d deutsch Kong f inn Med* **34** 361, 1922

Keilmann<sup>57</sup> reported a case due to destruction of the hypophysis by a large cyst weighing 93 Gm. Kiyono<sup>65</sup> also noted a case due to a hypophyseal cyst.

There is some evidence to believe that the case reported by Hochstetter and Veit<sup>66</sup> had as its pathologic basis a lipoid granuloma of the type found in the Hand-Schüller-Christian syndrome.<sup>67</sup>

Von Gerlóczy<sup>68</sup> reported the appearance of cachexia and anemia in a pituitary dwarf who had been subjected to intensive irradiation of the hypophyseal region. However, Gordon Holmes<sup>69</sup> and Julius Bauer<sup>6</sup> noted the spontaneous appearance of Simmonds' disease in pituitary dwarfs.

Destruction of the pituitary gland by a metastatic abscess has been noted in a case of hypophyseal cachexia by Jungmann.<sup>46b</sup> Hirsch and Berberich<sup>70</sup> reported a case due to destruction of the gland by hemorrhage.

Reye<sup>36</sup> expressed the belief that pituitary atrophy is secondary more commonly to thrombosis than to embolism, especially in cases without definite sepsis.

Maresch<sup>34</sup> called attention to the fact that the appearance of hypophyseal cachexia is common after repeated labors, particularly if they follow in close succession, and suggested a functional exhaustion of the pituitary gland as a cause for the syndrome.

In Riese's case<sup>71</sup> the mother of the patient had had symptoms suggestive of pituitary disease, and the author suggests that there may be a constitutional weakness of the pituitary gland which becomes obvious if it is subjected to great strain as in repeated pregnancies.

So much for the pathologic changes found in the hypophysis itself in Simmonds' disease. There is usually associated a secondary atrophy of the thyroid, gonads and suprarenal cortex. This may, however, be absent. Attention has already been called to the unusual smallness of the viscera or microsplachnia first noted by Simmonds. Meng<sup>72</sup> was able to demonstrate marked atrophy of the hair follicles and sweat glands in his case of pituitary cachexia. Altmann<sup>73</sup> called attention to the common association of some degree of pulmonary tuberculosis with Simmonds' disease.

65 Kiyono, H. *Virchows Arch f path Anat* **252** 118, 1924.

66 Hochstetter, F. *Med Klin* **18** 647, 1922. Veit, B. *Frankfurt Ztschr f Path* **28** 1, 1922.

67 Chester, W. *Virchows Arch f path Anat* **279** 561, 1930.

68 von Gerlóczy, G. *Klin Wchnschr* **2** 902, 1923.

69 Holmes, Gordon. *Brit M J* **2** 1037, 1926.

70 Hirsch, S., and Berberich, J. *Klin Wchnschr* **3** 483, 1924.

71 Riese, H. *Med Welt* **3** 1546, 1929.

72 Meng, H. *Frankfurt Ztschr f Path* **36** 650, 1928.

73 Altmann, F. *Frankfurt Ztschr f Path* **36** 393, 1928.

When a distinct clinical syndrome accompanies the destruction of the anterior lobe of the hypophysis, it assumes the form described by Simmonds. However, there can be extensive, almost complete destruction of the pituitary gland, and no characteristic symptoms may be noted. Such destruction of the hypophysis without clinical symptoms has been noted by Markel,<sup>50</sup> Krumbhaar,<sup>74</sup> Woims and Delater,<sup>26</sup> Kiyono<sup>75</sup> and Broussilovski<sup>76</sup>

Although it is quite obvious that the syndrome of Simmonds' disease depends on the absence of the anterior lobe of the hypophysis, no one has attempted to correlate the disease with any one of the three specific cells found in the pituitary.

It is now established that acromegaly depends on the hyperactivity of the eosinophilic elements, and it is perhaps not unlikely that Simmonds' disease has as its physiologic basis a *hypofunction* of these same cells. At least, one might expect something of this nature from the directly opposite clinical pictures presented by acromegaly and Simmonds' disease.

It is unlikely that the basophilic cells have any relation to the syndrome. The presence of a large number of these cells in an adenoma (Simmonds) was unable to protect against the development of the clinical picture.

Another clinical observation implicating the eosinophilic cells is to be found in the course of some cases of acromegaly. These start as typical acromegalias and then later asthenia, cachexia, loss of gonadal function and loss of pubic and axillary hair develop and the patients finally die in extreme cachexia. In these patients it seems logical to postulate an exhaustion of the previously hyperactive eosinophilic tissue as the cause for the appearance of the features suggesting Simmonds' syndrome.

In the future it would be advisable to utilize every opportunity to study the relative proportion of the various cells in all cases of Simmonds' disease to see whether an eosinophilic deficiency is the basis of the syndrome.

#### PATHOLOGIC PHYSIOLOGY

The entire knowledge regarding the relation of the pituitary gland to clinical medicine is quite recent. Although Marie<sup>77</sup> first recognized acromegaly as a clinical picture, it was Minkowski<sup>78</sup> who first associated this syndrome with a lesion of the pituitary body. In 1894,

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74 Krumbhaar, E. B. *M. Clin. North America* **5** 927, 1921.

75 Kiyono, H. *Virchows Arch. f. path. Anat.* **259** 388, 1926.

76 Broussilovski, L. *Encéphale* **20** 734, 1925.

77 Marie. *Rev. de med.* **6** 297, 1886.

78 Minkowski. *Berl. med. Wchnschr.* **24** 371, 1887.

Tamburini<sup>79</sup> recorded the common association of changes in the eosinophilic cells of the anterior lobe with acromegaly. Since this time acromegaly has been considered as a hyperfunction of the anterior lobe, or at least part of it. Recently, Putnam, Benedict and Teel<sup>80</sup> have been able to produce acromegaloid features in dogs by the injection of extracts from the anterior lobe.

Until Simmonds no one believed that there was a clinical picture associated with a lowered or absent function of the anterior lobe. I believe it has been shown that Simmonds' contention was correct and that one should consider the relationship between acromegaly and Simmonds' disease in the same light that myxedema and hyperthyroidism or tetany parathyreopriva and osteitis fibrosa of Recklinghausen are viewed. It is necessary to recall only that acromegaly is characterized by overgrowth, splanchnomegaly and increase in the size of the pituitary gland, whereas pituitary cachexia is marked by cachexia, micro-splanchnia and destruction of the gland.

The classic experiments of Cushing<sup>81</sup> and his school showed that after hypophysectomy in dogs there intervened a state of "cachexia hypophyseopriva," characterized by failure to grow, loss of weight and gonadal atrophy. Although it is true that Camus and Roussy<sup>82</sup> and Bailey and Bremer<sup>83</sup> have adduced evidence to show that many of the findings attributed by Cushing to the removal of the pituitary may have been a result of injury to the hypothalamic region, yet it is a fact that hypothalamic damage does not explain all Cushing's findings. The recent work of Smith<sup>84</sup> in which, by a new technic, he was able to excise the pituitary in rats without the possibility of injury to the midbrain shows that cachexia and genital atrophy are direct consequences of removal of the pituitary gland. Smith<sup>85</sup> could also produce in his rats a distinct premature senility that recalls the picture seen clinically in Simmonds' disease.

Goetsch<sup>12</sup> has noted that in the operative removal of the anterior lobe of the pituitary there is a permanent decrease in the number of Leydig's cells and a lack of spermatogenesis. This information, coupled

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79 Tamburini. Riv sper di freniat **20** 559, 1894.

80 Putnam, T. J., Benedict, E. B., and Teel, H. M. Studies in Acromegaly. VIII. Experimental Canine Acromegaly Produced by Injection of Anterior Lobe Extract, Arch Surg **18** 1708 (April) 1929.

81 Cushing, H. Bull Johns Hopkins Hosp **21** 127, 1910.

82 Camus, J., and Roussy, G. Endocrinology **4** 507, 1920.

83 Bailey, Percival, and Bremer, Frederic. Experimental Diabetes Insipidus, Arch. Int. Med **28** 773 (Dec.) 1921.

84 Smith. Anat Rec **32** 221, 1926.

85 Smith, P. E. Disabilities Caused by Hypophysectomy and Their Repair, J. A. M. A **88** 158 (Jan. 15) 1927.

with the recent work of Zondek and Ascheim, leaves no doubt that the anterior lobe is the "motor" of the gonads and that normal sexual function depends on an intact pituitary gland. It is now quite clear why cases of Simmonds' disease show symptoms of lowered sexual activity. Early loss of menses, sterility, loss of libido and gonadal atrophy as they occur in this disease are probably the result of the absence of the stimulus that is normally supplied by the anterior pituitary lobe.

The relationship of the anterior lobe of the pituitary gland to the basal metabolic rate cannot be said to have been completely studied. However, there is good clinical evidence to show that lesions in this region give rise to a depression of the basal metabolic rate<sup>86</sup>. In fact, readings lower than those found in complete myxedema have been reported.

Plaut<sup>41</sup> studied three cases of pituitary cachexia and found the metabolism depressed in all. As a result of her extensive investigation she gives the following tabulation:

Disease	Basal Metabolic Rate	Specific Dynamic Value
Starvation	Normal or low	Low
Hypophyseal obesity	Normal	Low
Hypophyseal cachexia	Low	Low
Myxedema	Low	Normal
Exophthalmic goiter	High	Variable
Usual cachexias	High	Unknown
Constitutional underweight	Normal	Increased

Plaut points out that the basal metabolic rate may be a useful aid in differentiating the cachexia of pituitary origin from that due to carcinoma, tuberculosis and other conditions. In these states the basal rate is always elevated, but in Simmonds' disease it is always reduced, often to extreme levels. Høbboll<sup>87</sup> reported that sixteen of nineteen patients with carcinomas of the gastro-intestinal tract had an elevation of the basal metabolic rate. The highest level recorded was plus 51.3 per cent. Strieck and Mulholland<sup>88</sup> noted a basal metabolic rate of plus 58 per cent in a case of metastasizing carcinoma of the stomach.

It should be noted, however, that some observers have noted a low basal metabolic rate in cachexia not of pituitary origin. Joslin<sup>89</sup> reported the cases of emaciated diabetic patients with basal rates of minus 40 per cent.

<sup>86</sup> Buentin, J. *Physiol.* **71**, xxvii, 1931. Reye<sup>36</sup>, Zondek<sup>43</sup>.

<sup>87</sup> Høbboll, S. A. *Acta med. Scandinav.* **72**, 475, 1929.

<sup>88</sup> Strieck, F., and Mulholland, H. B. *Deutsches Arch. f. klin. Med.* **162**, 51, 1928.

<sup>89</sup> Joslin, E. P. *The Treatment of Diabetes Mellitus*, ed. 3, Philadelphia, Lea & Febiger, 1923.



In regard to changes in the specific dynamic value of the food-stuffs, the findings are not so constant. Kestner, Liebeschütz-Plaut and Schadow<sup>45</sup> expressed the belief that there is always a depression in Simmonds' disease. Other observers<sup>6</sup> have not been able to confirm these findings. In hypophysectomized rats, Smith<sup>90</sup> found the specific dynamic action of the proteins to be absent. Evidence to support the rôle of the pituitary in the determination of the basal metabolic rate is to be had from the cases of Simmonds' disease in which the patients were treated with active extracts from the anterior lobe. An increase in the consumption of oxygen from 69 cc per minute to 149.2 cc per minute has been recorded.<sup>91</sup> It is interesting that Knipping<sup>92</sup> found that the specific dynamic action of the protein was always decreased during pregnancy. He suggests that this may be associated with the pituitary changes that occur at this time and may possibly be due to a redistribution of the pituitary cells.

Zondek and Maix<sup>46a</sup> were able to demonstrate distinct disturbances in the ability of patients with pituitary cachexia to excrete water and salt normally.

Changes in the growth of body hair have been noted in Simmonds' disease since the original description. In this connection it is interesting to note that Benedict, Putnam and Teel<sup>93</sup> were able to show that there were disturbances in the growth of the hair of dogs after hypophysectomy.

Schellong<sup>94</sup> has recently pointed out that the attacks of collapse and unconsciousness so often observed in Simmonds' disease are the result of the sudden drop in blood pressure that follows exertion in these patients, even if the original blood pressure level is normal. Schellong believes that this paradoxical blood pressure reaction is a symptom of insufficiency of the anterior pituitary lobe and a valuable aid in diagnosis. This observation is interesting and should be confirmed.

#### THERAPY

As in most other conditions in which the clinical course is irregular, the evaluation of any one form of therapy offers difficulties. When one recalls that untreated patients may live as long as forty-four years<sup>95</sup>

90 Foster, G. L., and Smith, P. E. Hypophysectomy and Replacement Therapy, *J. A. M. A.* **87** 2151 (Dec. 25) 1926.

91 Zondek, H. *Die Krankheiten der Endokrinen Drüsen*, Berlin, Julius Springer, 1923.

92 Knipping, H. W. *Arch. f. Gynak.* **116** 520, 1923.

93 Benedict, E. B., Putnam, T. J., and Teel, H. M. *Am. J. M. Sc.* **179** 489, 1930.

94 Schellong, F. *Klin. Wchnschr.* **10** 100, 1930.

95 Reiche, F. *Med. Klin.* **26** 1447, 1930.

after the onset of symptoms, one must regard with caution statements regarding benefits derived from any special form of therapy

In his original descriptions Simmonds pointed out that replacement therapy with the anterior lobe of the pituitary was indicated and should be tried. This, in the form of prephyson, has yielded excellent results in the hands of Reye, Zondek and Lichtwitz. However, the results do not seem conclusive enough to enable one to speak of a "specific" for this disease in the manner that one regards thyroid extract in the treatment of myxedema.

If syphilis is present, it should be treated vigorously, as recession of the clinical picture under antisyphilitic therapy has been observed.

An expanding intracranial tumor compressing the anterior pituitary lobe may often be approached surgically, and temporary alleviation, at least, is offered.

To combat the extreme cachexia and anorexia that is present in this disease, general hygienic and dietetic measures should be followed. In addition, the careful administration of insulin (Falta) in doses of from 2 to 20 units subcutaneously one-half hour before meals may be a useful aid in increasing the weights of the patients.

As the disease often appears post partum, usually in cases with obstetric complications, it would seem logical to advise careful management of the delivery and puerperium by a competent obstetrician to avoid this complication.

#### SUMMARY

Attention has been called to a syndrome not frequently encountered in the English literature and one that I believe to be more common than is generally accepted. In its fully developed form it is readily recognized by the association of extreme cachexia with signs and symptoms of gonadal atrophy. The onset is often consequent on a complicated labor, and among the clinical features may be mentioned premature aging, early and complete amenorrhea, loss of pubic and axillary hair, atrophy of the lower jaw with loss of teeth and a profound depression of the basal metabolic rate.

In addition to the advanced obvious cases, attention should be directed to mild, abortive forms that masquerade under such diagnoses as arteriosclerotic cachexia, syphilitic cachexia and latent tuberculosis.

The physiologic significance of disease in the pituitary region is great, and much can be learned from observing closely patients presenting signs of pituitary cachexia.

Dr B S Oppenheimer, physician to Mount Sinai Hospital, from whose service the case reported came, has made this publication possible. Dr J H Globus, neuropathologist to the hospital, allowed me to use the sections and gave many helpful suggestions. Dr R T Frank supplied figure 4.

# EXPERIMENTAL EDEMA IN NEPHRECTOMIZED DOGS

## II THE RÔLE OF WATER AND CHLORIDES

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CHICAGO

Lyon, Shafton and Ivy<sup>1</sup> found that it was possible to produce edema in bilaterally nephrectomized dogs and at the same time to prolong the life of such animals by the subcutaneous administration of Ringer's solution. It was observed that on the second or third day vomiting and diarrhea resulted, which led to dehydration and hypochloremia. The Ringer's solution relieved this condition and presented water and chlorides for the formation of edematous fluid.

The following questions naturally arose from this work. Which was most important in the production of the edema, water or chlorides? Was the edema, possibly by acting to dilute "toxins," responsible for the prolongation of life, or was the prolongation of life due simply to the relief of the dehydration and hypochloremia? We desired to answer these questions and believed that the water factor could be controlled by the use of a solution of dextrose instead of Ringer's solution, and that the chloride factor could be controlled by adding various amounts of Ringer's solution to the solution of dextrose. Our results show that the water alone is not responsible for the edema, and that edema is not necessary for the prolongation of life.

### METHODS

In these experiments healthy dogs varying in weight from 35 to 50 pounds (from 1,600 to 2,300 Gm) were subjected to bilateral nephrectomy. The operations were performed under strict asepsis, with ether anesthesia, the kidneys were removed through an abdominal incision. The solutions injected were Ringer's solution (consisting of sodium chloride, 0.9 per cent, potassium chloride 0.042 per cent, calcium chloride, 0.024 per cent, and sodium bicarbonate, 0.02 per cent) and a 4 per cent solution of dextrose specially prepared for intravenous injections. The solutions and apparatus were sterilized before use. The regular laboratory diet was offered to the dogs each day. Blood drawn for analysis and venesection was

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1 Lyon, E. E., Shafton, A. L., and Ivy, A. C. Arch. Int. Med. **44**: 424 (Sept.) 1929

taken from the saphenous vein by needle and syringe Hypodermoclysis was performed in the scapular region

The volume of solution injected varied from 1,500 to 2,000 cc, i e, about 90 cc per kilogram This volume was arrived at by observing the daily water intake of large dogs and by approximating the amount of water lost in the vomitus, stools and respiration That it was not excessive is seen from the experimental results given in the following paragraphs

### EXPERIMENTS AND RESULTS

Seven groups of experiments were performed in this study

TABLE 1—*Results of Administration of Ringer's Solution Subcutaneously to Nephrectomized Dogs*

No	Lived, Hours	Anasarca, Day	Ascites, Cc	Hydro- thorax, Cc	Hydro- peri- cardium, Cc	Diarrhea, Day	Vomiting, Day	Salivation, Day
1*	158	4th				4th	4th	None, no autopsy
2	110	3d	50	20	20	4th	3d	None
3	123	4th	40	10	25	5th	2d	5th
4	167	5th	1,200	None	15	3d	2d	None
5	130	4th	175	40	4	4th	5th	None
6	231	3d	1,800	75	15	4th	2d	7th
7	221	6th	50	20	10	5th	3d	None
8	158	4th	100	20	3	3d	4th	None
9	108	4th	None	None	None	3d	3d	3d
Average	156.2							

\* Dog removed before autopsy was made

TABLE 2—*Showing that Water Alone Does not Produce Edema in Bilaterally Nephrectomized Dogs\**

No	Lived	Anasarca	Salivation	Diarrhea, Day	Vomiting Day	Change in Weight, Pounds
1	92 hrs, 40 min	None	None	None	2d	Lost 2 (900 Gm)
2	104 hrs, 45 min	None	None	None	2d	Lost 1.5 (700 Gm)
3	137 hrs	None	None	4th	4th	
4	94 hrs, 30 min	None	None	2d	None	
5	87 hrs, 48 min	None	3d day, slight	2d	None	
Average	103 hrs					

\* Group 3, these dogs received from 1,500 to 2,000 cc of a 4 per cent solution of dextrose daily by hypodermoclysis

GROUP 1—The dogs in this group were given no postoperative treatment and served as controls There were five dogs in the group, the length of life being from 65 to 154 hours The average length of life was 108.8 hours, which compares favorably with the average of 105 hours obtained by Lyon, Shafton and Ivy

GROUP 2—The dogs in this group were given from 1,500 to 2,000 cc of Ringer's solution subcutaneously each day There were nine dogs in the series, the length of life being from 108 to 231 hours, with an average of 156.2 hours The results are recorded in table 1

Edema developed in all the dogs, ascites and hydropericardium developed in all but two, and hydrothorax developed in all but three The average length of life was prolonged

GROUP 3—The dogs in this group were given subcutaneous injections of from 1,500 to 2,000 cc of a 4 per cent solution of dextrose daily. They lived from 88 to 137 hours. The average length of life was 103 hours. There were five dogs in the group. The results are recorded in table 2. Edema developed in none of the dogs of this group. The average length of life was not prolonged, this shows that dehydration is not the cause of early death in nephrectomized dogs, because these dogs were not dehydrated and died in the same length of time as untreated nephrectomized dogs.

GROUP 4—These dogs (there were five dogs in the group) were given daily subcutaneous injections of from 1,500 to 2,000 cc of a 2:1 mixture of Ringer's solution and a 4 per cent solution of dextrose. The results are recorded in table 3.

TABLE 3—*Results with a Mixture of Two Thirds of Ringer's Solution and One Third of a 4 Per Cent Solution of Dextrose Subcutaneously Administered to Nephrectomized Dogs*

No	Lived, Hours	Anasarca	Ascites Cc	Hydrothorax, Cc	Hydropericardium, Cc	Diarrhea, Day	Vomiting, Day	Salivation, Day	Blood Chlorides
1	120	None	None	None	2	Slight, 4th	None	None	0.481 0.556
2	127½	All legs, serotum and chest	100 fluid	10, each side	3, clear fluid	5th	4th	None	0.478 0.498
3	223	General, 6th day	200	15, each side	25, clear fluid	6th	5th	9th	0.478 0.490
4	130	None	None	10, each side	None	None	None	None	
5	206	None	None	None	2	6th	6th	6th	0.469 0.525
Aver 161									

Blood was drawn from the saphenous vein daily for analysis. The blood chlorides were found either to remain normal or to show a slight increase. In two dogs a general edema with ascites developed. The average length of life was prolonged.

GROUP 5—There were nine dogs in the series. They were given daily injections of from 1,500 to 2,000 cc of a 1:2 mixture of Ringer's solution and a 4 per cent solution of dextrose. The results are recorded in table 4.

The average length of life was 161 hours, that is, life was prolonged. Only one dog showed any sign of edema of the skin, and that was very slight, while three showed ascitic fluid, six hydropericardial fluid, and one, fluid in the pleural cavity. The blood chlorides, which were followed in five animals, were normal or somewhat reduced.

GROUP 6—There were three dogs in the series, the length of life being from 91 to 239 hours. They were given daily injections of 1,500 cc of equal amounts of a 4 per cent solution of dextrose and Ringer's solution. Edema (550 cc of ascitic fluid) was seen in but one of the three, and only after the fifth day postoperatively. The chlorides were followed, and were observed to remain practically normal.

TABLE 4—*Results on Administration of a Mixture of One Thud Ringer's Solution and Two Thuds of a 4 Per Cent Solution of Dextrose*

No	Lived, Hours	Anasarca	Ascites, Cc	Hydro thorax, Cc	Hydro peri cardium, Cc	Diarrhea, Day	Vomiting, Day	Sal- vation, Day	Blood Chlorides
1	124	None	None	None	None	None	None	4th	
2	228	None	25	None	15	6th, until death	6th, until death	7th, until death	
3	100	None	None	None	15	3d, until death	2d, until death	2d, until death	
4	91	None	15	None	None	None	None	None	
5	93	None	None	None	5	None	None	None	0 467
6	90	Very slight, of scrotum	None	None	5	None	None	None	0 304
7	227	None	25	10	125	8th, until death	6th, until death	8th, until death	0 353
8	248	None	None	None	None	5th, until death	6th, until death	6th, until death	0 504
9	255	None	None	10	3	5th, until death	4th, until death	4th, until death	0 488
Aver	161								

TABLE 5—*Effect of Venesection Plus Ringer's Solution (Group 7)*

No	Lived, Hours	Anasarca, Day	Ascites	Hydro thorax	Diarrhea, Day	Vomiting, Day	Salvation, Day	Weight, Pounds
1	147	6th	Present	Present	None	5th	6th	Gained 5 5 (2,500 Gm )
2	108	None	None	None	4th	4th	None	
3	158	4th, fore legs	None	None	5th	5th	None	
4	250	4th, fore legs	Present	Present	4th	4th	8th	Gained 18 (8,200 Gm )
Average	165 6							

TABLE 6—*Summary of Results*

Group	No of Dogs	Procedure	Length of Life, Hours	Edema
1	5	Control (bilateral nephrectomy)	108 8	Not produced
2	9	Bilateral nephrectomy and Ringer's solu tion subcutaneously	156 2	Produced
3	5	Bilateral nephrectomy and a 4 per cent solution of dextrose subcutaneously	103	Not produced
4	5	Bilateral nephrectomy and a mixture of Ringer's solution and a 4 per cent solu tion of dextrose, 2 1, subcutaneously	161	Produced in 2 of 5
5	9	Bilateral nephrectomy and a mixture of a 4 per cent solution of dextrose and Ringer's solution, 2 1, subcutaneously	161	Produced in 1 of 9
6	3	Bilateral nephrectomy and a mixture of equal amounts of Ringer's solution and a 4 per cent solution of dextrose sub cutaneously	158 6	Produced in 1 of 3
7	4	Bilateral nephrectomy and Ringer's solu tion subcutaneously, with venesection, daily	165 6	Produced in 3 of 4

GROUP 7—There were four dogs used in the experiment. They were given daily 1,500 cc of Ringer's solution subcutaneously, and venesection was done, the amount of blood being from 40 to 100 cc daily. The dogs lived from 108 to 250 hours. Table 5 shows the results.

Edema developed in three of the four dogs, and two showed ascites and hydrothorax. Two dogs showed a gain in weight. Venesection was not of any appreciable benefit.

#### COMMENT ON RESULTS

In the first or control group of untreated, bilaterally nephrectomized dogs the average length of life was found to be 108.8 hours, which compares closely with the observation of Lyon, Shafton and Ivy, of 105.6 hours.

In the second group the average length of life was found to be 156.2 hours with the subcutaneous administration of the Ringer's solution, as compared with 165 hours for the animals in Lyon's series when the same procedure was followed.

In the third group, a 4 per cent solution of dextrose was administered subcutaneously in order to observe the effect of a volume of water equal to that given in Ringer's solution without the salt factor, the dextrose being oxidized. It was found that there was no production of edema, and that the length of life was practically that of the untreated dogs, or 103 hours.

In the fourth, fifth and sixth groups, mixtures of Ringer's solution and a 4 per cent solution of dextrose were given in an attempt to determine the amount of salt required to produce edema. The question is whether edema will develop if salts are replaced sufficiently to balance the amount lost by vomiting and diarrhea, or whether more than this amount is necessary. It was found that with the three mixtures of dextrose and Ringer's solution that were used, life was prolonged to the same extent as it was in the dogs receiving Ringer's solution only, but that there was a marked decrease in the edema produced, only four dogs showing any sign of edema. It is evident that if the chlorides, or salt factor, are controlled so that the blood chlorides remain about normal, edema does not result. In order to obtain edema, excess salt must be administered. Ringer's solution when administered alone provides the necessary excess salt.

In the seventh group, venesection was tried, with the injection of Ringer's solution in an attempt to remove some of the toxic products that might have accumulated. The amount of blood lost was amply replaced by Ringer's solution. The average length of life of the dogs in this group was 165.6 hours or slightly but not significantly longer than those treated with Ringer's solution alone in our experiments, and practically the same as those treated with Ringer's solution alone.

in Lyon, Shafton and Ivy's work. It is possible that the quantity of blood removed was not large enough, but it amounted to from one twenty-fifth to one tenth of the total blood volume daily.

These experiments demonstrate the important rôle that sodium chloride plays and the rather minor rôle that water and the products of nitrogenous retention play in the production of edema. In the presence of marked nitrogenous retention, water in "balanced" amounts is not retained in the body if the blood chlorides are subnormal. By keeping the input of water constant and controlling the input of sodium chloride in nephrectomized dogs, one can control the presence or absence of edema. There is apparently no strict relation between the level of the blood chlorides and the occurrence of edema, since edema may or may not be present with a normal level of blood chlorides, but in the absence of edema the blood chlorides are low. There is, however, a definite relation between the input of sodium chloride and the occurrence of edema.

These results, in our opinion, prove the contention of Widal<sup>2</sup> that although the retention of urea and other nitrogenous substances is responsible for uremia, it is not significant in the development of edema. We shall report evidence in a later paper to show that nitrogenous retention increases capillary permeability. Obviously, in these experiments we are dealing only with extrarenal factors.

The cause of death in nephrectomized dogs is unquestionably the retention of the substances normally eliminated by the kidneys. The fact that the nephrectomized dogs treated with a solution of dextrose alone did not live longer than untreated controls appears to indicate that dehydration per se is not an important contributory cause of death, since the dogs were receiving plenty of water. A loss of weight occurred in these dogs, which showed that no invisible retention of water occurred, whereas in the dogs which received the mixture of Ringer's solution and dextrose solution and in which edema did not occur the loss of weight was not so marked. It therefore appears that the dogs given dextrose solution were somewhat dehydrated, or that they could not retain the water because of a deficiency in sodium chloride. This indicates that the hypochloremia was the prime factor, that is, in order to obtain a retention of water adequate to prevent dehydration, sufficient sodium chloride had to be given to prevent hypochloremia, if an excess was given, edema resulted. We therefore conclude that the prolongation of life is due primarily to maintenance of the normal balance of water, sodium and chlorides in the body, and not primarily to a dilution of the urinary or toxic substances retained. The slower rate

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<sup>2</sup> Widal, F., and Lemierre, A. *Bull. et mém. Soc. méd. d'hôp. de Paris* 20:785, 1903.



of accumulation of nitrogenous products, as shown by the analysis of the blood of dogs treated with Ringer's solution in the work of Lyon, Shafton and Ivy, is most probably due to the absence of dehydration, which is known to increase the nitrogenous content of the blood, because it is probable that dehydration per se promotes proteoclastic changes in the cells

Our results indicate not only that the intake of sodium chloride should be limited in nephritis, a well known fact, but also that if a patient with nephritis has vomited so much that hypochloremia exists, which is probably rare, the patient should be benefited by the proper or controlled administration of dextrose and sodium chloride

#### CONCLUSIONS

1 Ringer's solution (from 1,500 to 2,000 cc for dogs weighing from 35 to 50 pounds [from 1,600 to 2,300 Gm ]) injected subcutaneously in bilaterally nephrectomized dogs produces edema and prolongs life for an average of sixty hours

2 A similar volume of a 4 per cent solution of dextrose injected subcutaneously into bilaterally nephrectomized dogs neither prolongs life nor produces edema

3 The same volume of mixtures of Ringer's solution and a 4 per cent solution of dextrose, containing sufficient salt to maintain the blood chlorides at a normal level, does not produce edema consistently when injected subcutaneously into bilaterally nephrectomized dogs. It does, however, prolong life

4 Venesection (from  $\frac{1}{25}$  to  $\frac{1}{10}$  of total volume of blood daily) did not prolong the life of nephrectomized dogs receiving Ringer's solution

5 Our results show that the prolongation of life is due primarily to maintenance of the normal water-sodium-chloride balance in the body, and not to a dilution by edematous fluid of the urinary or toxic substances retained

6 Edema does not occur in bilaterally nephrectomized dogs until water with excessive sodium chloride is supplied

7 The retention of urinary products per se in the presence of hypochloremia (chiefly sodium chloride) is not conducive to edema, even when adequate water is supplied, this confirms the contention of Widal

# INFLUENCE OF THE PITUITARY GLAND ON ERYTHROCYTE FORMATION

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DETROIT

In this article we shall endeavor to show that (a) The pituitary secretion has a very important influence on erythrocyte formation (b) *Primary* disease of the suprarenal cortex results in *secondary* pituitary changes, thus accounting for many signs and symptoms erroneously ascribed to the suprarenal cortex (c) The specific and selective embryo-hormonic relations of the pituitary gland to mesodermal tissues is a reasonable explanation for the polymorphic signs and symptoms of pituitary disturbances

Two cases of polycythemia vera with pituitary basophilism, coming to autopsy, and polycythemias experimentally induced in dogs by bilateral adrenalectomy form the basis of our report

Our interest in the erythropoietic function of the pituitary was the result of some clinical observations which pointed to this gland as the major factor in stimulating the hematopoietic system to erythrocyte formation

While we were engaged in carrying out the experimental part of the work, a splendid article by Cushing<sup>1</sup> appeared, in which he reported twelve cases of pituitary basophil adenomas, associated with, among other things, a tendency to polycythemia Two were his own, the remaining ten being reported by others (Turney, Anderson, Riechmann, Zondek, Parkes-Weber, Teel, Friedman, Mooser, Raab-Krause and Wieth-Pedersen) Death occurred in nine cases, eight of which came to autopsy A basophilic adenoma of the pituitary was found in three cases, an undifferentiated adenoma in two cases and an adenomatous-like structure in a fibrosed area of the anterior pituitary in one case, two patients were said to be "normal"

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1 Cushing, H The Basophil Adenomas of the Pituitary Body and Their Clinical Manifestations (Pituitary Basophilism), Bull Johns Hopkins Hosp 50 137, 1932

Cushing gave the following features as characteristic of all cases

(1) A rapidly acquired, peculiarly disposed and usually painful *adiposity* (in one instance representing a 40 per cent gain in weight), confined to the face, neck and trunk, the extremities being spared, (2) a tendency to become *round-shouldered* (kyphotic) even to the point of measurable loss of height associated with lumbo-spinal pains, (3) a sexual dystrophy, shown by early *amenorrhea* in the females and ultimate *impotence* in the males, (4) an alteration in normal hirsuties, shown by a tendency to *hypertrichosis* of the face and trunk in all the females as well as in preadolescent males and possibly the reverse in adult males, (5) a dusky or plethoric appearance of the skin with *purplish lineae atrophicae*, (6) *vascular hypertension*, (7) a tendency to *erythema*, (8) variable *backaches*, *abdominal pains*, *fatigability* and ultimate extreme *weakness*

That certain cerebral conditions may lead to polycythemia is becoming recognized with greater frequency Gunther<sup>2</sup> stated that certain clinical observations lead to the question whether or not there is a cerebral regulating center for the blood-forming organs He said that it is within the range of possibilities that the working mechanism of this center stands in relationship to the endocrine system, so that a physiologic separation is hardly possible He reports a case of cerebral polycythemia in a 26 year old man with marked obesity, hypotrichosis, hyposexuality, headaches, vasomotor upsets, respiratory disturbance, narcolepsy and psychic disturbances The spleen was not enlarged, and there was no hypertension

Etiologically Gunther considered that the condition is due to a basal disturbance between the third ventricle and the hematopoietic system, the exact nature of which is still in doubt Furthermore, he said that there is a close relationship between the endocrine system, particularly the suprarenals, so that at present it is impossible to decide whether the condition is a primary cerebral or an endocrine disturbance

Guillain, Lechelle and Garcin<sup>3</sup> reported five cases of polycythemia which seemed to originate in the region of the pituitary and tuber cinereum This report was based on clinical symptoms usually associated with disturbances in and around the pituitary

Nathan<sup>4</sup> recently called attention to the diencephalic area as possibly being responsible for polycythemia

Castex<sup>5</sup> believes that Geisbock's disease (polycythemia with hypertension) is probably a diencephalic syndrome

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2 Gunther, Hans Ueber zerebrale Polyglobulie, Deutsches Arch f klin Med **16** 41, 1930

3 Guillain, G, Lechelle, P, and Garcin, R La polyglobulie de certains syndromes hypophysaires et hypophyso-tuberienes, Compt rend Soc de biol **106** 515, 1931

4 Nathan, M Erythremies protopathiques et diencephale, Presse med **39** 403, 1931

5 Castex, M R La hypertension arterial, Buenos Aires, Humberto Andre-cetta, 1929

Schulhof's and Matthies' <sup>6</sup> work on polycythemia of cerebral origin was stimulated by Schulhof's observations in 1920, when he noticed polycythemia in cases of epidemic encephalitis. These authors found that polycythemia of long duration, induced by a lesion of the proximal part of the vegetative centers of the brain in rabbits, indicates that the brain plays a rôle in the regulation of the numbers of circulating erythrocytes. They further stated that a humoral or endocrine intervening mechanism is not impossible. Hecht and Weil <sup>7</sup> found that concussion of the brain was at times accompanied by polycythemia.

Lichtwitz <sup>8</sup> reported a case of encephalitis with polycythemia and also a case of acromegaly with polycythemia.

A familial tendency toward polycythemia is not uncommon. Doll and Rothschild <sup>9</sup> reported a familial tendency toward polycythemia in conjunction with Huntington's chorea. Gutzeit <sup>10</sup> reported cases of polycythemia in two sisters and also in a patient who had a son suffering from lymphatic leukemia. Klumpp and Hertig <sup>11</sup> reported cases presenting a composite picture of both polycythemia and myelogenous leukemia.

Engelking <sup>12</sup> found eleven cases of the Vaquez form of polycythemia in three generations of one family. Tancre <sup>13</sup> also reported a familial tendency toward this condition.

Polycythemia with narcolepsy is not infrequent, as mentioned by Neisser, <sup>14</sup> Munzer, <sup>14</sup> Kraus <sup>14</sup> and Jolly <sup>14</sup>.

We have a case under observation at the present time. The relationship of the pituitary and the third ventricle area to narcolepsy has been frequently emphasized (Fulton and Bailey <sup>15</sup>). It is not surprising,

6 Schulhof, K., and Matthies, M. M. Polyglobulia Induced by Cerebral Lesions, *J. A. M. A.* **89** 2093 (Dec 17) 1927.

7 Hecht, P., and Weil, P. Polycythämie und Hirnerschütterung, *Aerztl. Sachverst.-Ztg.* **35** 35, 1929, *Deutsche med. Wchnschr.* **55** 380, 1929.

8 Lichtwitz, L. Hypophysäre Symptome und Hypophysenkrankheiten, *Verhandl. d. deutsch. Gesellsch. f. inn. Med.* (Kong. 42) 1930, p. 35.

9 Doll, H., and Rothschild, K. Familiäres Auftreten von Polycythämia rubra im Verbindung mit Chorea progressiva hereditaria Huntington, *Klin. Wchnschr.* **52** 2580, 1922.

10 Gutzeit, K. Zur Pathologie und Genese der Polycythemia rubra, *Deutsches Arch. f. klin. Med.* **141** 30, 1922.

11 Klumpp, T. G., and Hertig, A. T. Erythremia and Myelogenous Leukemia, *Am. J. M. Sc.* **183** 201, 1932.

12 Engelking, E. Ueber familiäre Polycythemia, *Klin. Monatsbl. f. Augenh.* **64** 645, 1920.

13 Tancre, E. Zur Polycythemia rubra, *Deutsches Arch. f. klin. Med.* **123**. 435, 1917.

14 Quoted by Gunther <sup>2</sup>.

15 Fulton, J. F., and Bailey, P. Tumors in Region of Third Ventricle. Diagnosis and Relation to Pathological Sleep, *J. Nerv. & Ment. Dis.* **69** 1 (Jan.), 145 (Feb.), 261 (March) 1929.

therefore, that polycythemia is found in this condition if the pituitary is a factor in erythrocyte formation

Recently Houssay, Royer and Orias<sup>16</sup> found that in sixteen hypophysectomized rabbits the average hemoglobin content in 100 cc of blood equaled 11.56 Gm, whereas twelve normal rabbits had an average hemoglobin content of 13.6 Gm. The red cells were also diminished in the hypophysectomized animals, but the authors called attention to the marked variation in the red cell count of normal animals. Collin and Baudot,<sup>17</sup> from their work on the guinea-pig, concluded that the embryonic pituitary has a hematopoietic function. Watrin,<sup>18</sup> from his studies, believes that there are erythropoietic centers in the pituitary of the pregnant guinea-pig.

Moldawsky<sup>19</sup> believes that glandular disturbances produce stimulation of bone marrow, and that there is a constant hormone present in the blood stream which excites this stimulation. He cited various endocrine disturbances to prove this. He based his conclusions on eighty patients suffering from various endocrine diseases, such as exophthalmic goiter, myxedema, tumors of the pituitary, acromegaly and pituitary dystrophy. In order to keep the red cells constant, he said, there must be a hormone present which stimulates the formation of blood. He did not believe that any one gland specifically stimulates the red bone marrow but thought that the stimulation is the result of various hormones. He concluded that the red cells give an indication as to the function of the whole endocrine chain.

Falta, Bertelli and Schweeger,<sup>20</sup> giving posterior lobe extract by the hypodermic method, found an enormous and long-standing increase of hemoglobin and erythrocytes, later followed by a decrease.

Polycythemia associated with tumors of the suprarenal is not uncommon, and it is our contention that the polycythemia in these cases is really of pituitary origin, as shown by our experiments and clinical cases.

Zucker<sup>21</sup> reported a case of tumor of the suprarenal cortex in a woman, 35 years old, with polycythemia. Postmortem examination

16 Houssay, B. A., Royer, M., and Orias, O. Hemoglobina y globulos rojos en los perros hipofisoprivos, *Rev. Soc. argent. de biol.* **7** 314, 1931.

17 Collin, R., and Baudot, J. Erythropoiese dans l'hypophyse, *Compt. rend. Soc. de biol.* **86** 596, 1922.

18 Watrin, J. Foyers d'erythropoiese dans l'hypophyse de cobaye gravide, *Compt. rend. Soc. de biol.* **87** 558, 1922.

19 Moldawsky, J. W. Ueber die Regulierung der Konstanz des roten Blutes, *Ztschr. f. klin. Med.* **114** 346, 1930.

20 Falta, W., Bertelli, and Schweeger. Ueber Beziehungen der inneren Sekretion zum Salzstoffwechsel, *Verhandl. der Kong. f. inn. Med., Wiesbaden*, 1909, p. 138.

21 Zucker, E. Maligner Nebennierenrindentumor mit Virilismus und Polycythämie, *Wien. klin. Wchnschr.* **42** 1045, 1929.

revealed carcinoma of the left suprarenal cortex, pulmonary metastasis, an enlarged spleen, an atrophic right suprarenal and a large left cardiac ventricle. No gross thyroid or pituitary change was found. This case, as well as others, shows the importance of making microscopic sections of the pituitary. Cushing<sup>1</sup> stressed the importance of this in his article on pituitary basophilism.

Redlich<sup>22</sup> reported the case of an 18 year old youth suffering from impotence, polyuria and obesity, who had a hypernephroma of the right suprarenal and atrophy of the left suprarenal. There was no polycythemia. The pituitary was markedly atrophic, weighing but 0.25 Gm as compared with the average normal weight of 0.63 Gm.

Schluter<sup>23</sup> described a case of hypernephroma of a 33 year old woman who had had amenorrhea for five years. The tumor was derived from the suprarenal cortex. The pituitary showed an increase in the eosinophilic cells with some decrease of basophil cells. Hypertension was also present. The ovaries were atrophic and fibrotic.

That the suprarenal is thought to have something to do with red cell formation is the opinion of several workers, but it is our contention that this is a specific pituitary function.

Schweizer<sup>24</sup> believes that the suprarenals influence centers which have a hematopoietic influence. If the suprarenals are defective, the central regulating mechanism is defective. He bases this conclusion in part on the observation of defects of the brain associated with suprarenal defects.

Huth<sup>25</sup> gave suprarenal cortex extract to patients suffering from various diseases, and seventeen of twenty-six cases showed a marked increase of red blood cells.

Pal<sup>26</sup> obtained excellent results with suprarenal cortex extract in various diseases (with respect to the red cell count). In pernicious anemia positive results were also recorded.

Soos<sup>27</sup> believes that in degeneration and necrosis of the suprarenal cortex, a toxin is formed which stimulates bone marrow. He thinks

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22 Redlich, F. Pluriglandulare Storungen bei einem Fall von Hypernephrom, *Med Klin* **26** 1255 (Aug 22) 1930.

23 Schluter, A. Hypernephroma-like Tumor of Left Suprarenal With Metastases to the Liver and Aplasia of the Right Suprarenal, *Frankfurt Ztschr f Path* **40** 97, 1930.

24 Schweizer, R. Die Nebenniere als Kontrollorgan fur die Blutkonstanz, *Schweiz med Wchnschr* **8** 633, 1927.

25 Huth, E. Ueber die Wirkung der Nebennierenrinde und des Histamins auf die Blutregeneration, *Wien klin Wchnschr* **42**:729, 1929.

26 Pal, J. Medical Furtherance of the Formation of Red Blood Cells, *Med Klin* **24** 1071, 1928.

27 Soos, J. Ueber die Korrelation der Epithelien und der Nebennieren im Lichte der Untersuchungen der Knochenmarksherde der Nebennieren, *Beitr z path Anat u z allg Path* **86** 444, 1931.

that there is a close relationship between the supra-renal cortex cells and the reticulo-endothelial system

Several workers found polycythemia after extirpation of the adrenals in animals

Szymonowicz<sup>28</sup> found polycythemia after this procedure Gradinescu<sup>29</sup> noted an increase of erythrocytes, averaging 28.5 per cent in dogs and 72 per cent in cats Dale<sup>30</sup> observed a concentration of the blood elements as did Donath<sup>31</sup>

Kellaway and Cowell<sup>32</sup> found an increase of hemoglobin and erythrocytes after extirpation of the supra-renal glands They believe that the changes in the concentration of the blood are dependent only on the damage to the supra-renal cortex

Stewart and Rogoff<sup>33</sup> did not find a constant change in the erythrocyte count, the relative increase of the serum was usually found on the day of death or just preceding it

Bazett<sup>34</sup> found a lessening of the blood volume and erythrocytes after adrenalectomy

Pende<sup>35</sup> noted a slight decrease of the erythrocytes and hemoglobin in young animals after adrenalectomy

Polycythemia in Addison's disease is not rare Rowntree and Snell<sup>36</sup> found polycythemia in Addison's disease In one hundred and eight cases the erythrocyte count ranged from 6,000,000 to 6,400,000 in one, from 5,000,000 to 5,400,000 in sixteen and from 4,500,000 to 4,900,000 in forty-three Twenty-two had hemoglobin values ranging from 80 to 89 per cent and three values from 90 to 99 per cent The average hemoglobin value in the one hundred and eight cases was 74.7

28 Szymonowicz, L Die Funktion der Nebennieren, Arch f d ges Physiol **64** 97, 1896

29 Gradinescu, A V Der Einfluss der Nebennieren auf den Blutkreislauf und den Stoffwechsel, Arch f d ges Physiol **152** 187, 1913

30 Dale, H H Conditions Which Are Conducive to the Production of Shock by Histamine, Brit J Exper Path **1** 103, 1920

31 Donath, quoted by Ehrmann, R, and Dunkin, L, in Hirsch, M Handbuch der inneren Sekretion, Leipzig, Curt Kabitzsch 1928, vol 3, p 283

32 Kellaway, C H, and Cowell, S J On the Concentration of the Blood and the Effects of Histamine in Adrenal Insufficiency, J Physiol **57** 82, 1923

33 Stewart, G N, and Rogoff, J, quoted by Bayer, G, in Hirsch, M Handbuch der inneren Sekretion, Leipzig, Curt Kabitzsch, 1928, vol 2, p 752

34 Bazett, H C Time Relations of Blood Pressure Changes after Excision of Adrenal Glands, With Some Observations on Blood Volume Changes, J Physiol **53** 320 (Feb 20) 1920

35 Pende, N Endocrinologia Patologia e clinica degli organi a secrezione interna, Milan, Francesco Vallardi, 1913

36 Rowntree, L G, and Snell, A M A Clinical Study of Addison's Disease, Philadelphia, W B Saunders Company, 1931

per cent, and the average erythrocyte count was 4,550,000. The authors said that anemia, in the restricted sense of the word that is now in vogue, is not common in Addison's disease.

The volume of the blood and plasma is usually normal in Addison's disease, except during the crises and terminal phases, according to these writers.

The value of the observations made on such a large series is obvious.

Polycythemia in Addison's disease was noted by early writers (Acuna,<sup>37</sup> Bramwell,<sup>38</sup> Christomanos,<sup>39</sup> Leva,<sup>40</sup> Rombach,<sup>41</sup> Vollbracht<sup>42</sup> and von Willebrand<sup>43</sup>). Of four cases of Addison's disease coming to autopsy at Harper Hospital since 1920, two showed polycythemia, unfortunately, reports on the pituitaries are not available.

#### RELATION BETWEEN SUPRARENAL CORTEX AND PITUITARY GLAND

From all of the available data, both clinical and experimental, which we possess, we are safe in saying that aplasia and hypoplasia of the pituitary are accompanied by aplasia and hypoplasia of the suprarenal cortex, whereas the reverse is found in hyperplasia of the pituitary. One of us (Dr Moehlig<sup>44</sup>) has discussed this relationship elsewhere. As Kraus<sup>45</sup> said, anomalies of the pituitary are most frequently found in anencephalia, hydrocephalus and other cerebral developmental anomalies. It has long been observed by older pathologists that when the anterior part of the brain is defective, aplasia of the suprarenal cortex and other developmental defects of this portion of the suprarenal

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37 Acuna, M. Enfermedad de Addison con hiperglobulia, Arch latino-am de pediat, 1905, cited in Folia haemat **3** 101, 1906.

38 Bramwell, B. A Case of Addison's Disease in Which a Great Improvement Took Place Under Open Air Treatment and Administration of Suprarenal Extract, Brit M J **2** 1082, 1905.

39 Christomanos, Anton. Ueber die Zahl der roten Blutkörperchen in zwei Fällen von Nebennierenerkrankung, Berl klin Wchnschr **36** 916, 1899.

40 Leva, J. Zur Lehre von Morbus addisonii, Virchows Arch f path Anat **125** 35, 1891.

41 Rombach, K. F. Morbus addisonii mit Polycythämie und Milztumor, Tijdschr v diergeneesk **1** 425, 1907.

42 Vollbracht, F. Fall von Morbus addisonii nach vorangegangener Purpura haemorrhagica mit einer Stoffwechseluntersuchung, Wien klin Wchnschr, 1899, p 737.

43 von Willebrand. Handlung Morbus addisonii mit Atrophie der Nebennieren, Finska lak-sällsk handl **47** 536, 1905.

44 Moehlig, R. C. The Pituitary Gland and the Suprarenal Cortex, Arch Int Med **44**:339 (Sept) 1929.

45 Kraus, E. J. Die Entwicklungsstörungen der Hypophyse, in Gruber, G. B. Die Morphologie der Missbildungen des Menschen und der Tiere, Jena, Gustav Fischer, 1929, vol 3, p 483.



were present We now know that this is due to primary pituitary involvement Smith,<sup>46</sup> Evans<sup>47</sup> and others have shown that hypophysectomy results in atrophy of the suprarenal cortex

Hyperplasia of the pituitary is accompanied by hyperplasia of the suprarenal cortex, as illustrated by experimental and clinical data<sup>44</sup> Putnam, Benedict and Teel,<sup>48</sup> Smith,<sup>46</sup> Evans,<sup>47</sup> Hofstatter,<sup>49</sup> Houssay,<sup>50</sup> Moehlig and Osius<sup>51</sup> and many others have been able to produce hypertrophy of the suprarenal cortex by injections of pituitary extract In hyperpituitarism we usually find hyperplasia of the suprarenal cortex This is true of the Cushing syndrome, described previously

Briefly, the suprarenal cortex reflects the state of the pituitary gland

Primary disease of the suprarenal cortex, resulting in either a hypofunction or hyperfunction, is accompanied by a variable, but nevertheless definite, secondary change in the pituitary We believe that this secondary change of the pituitary in response to primary disease of the suprarenal cortex explains many symptoms erroneously attributed to the suprarenal cortex Those persons predisposed to deficiency of the suprarenal cortex, for instance, constitutionally possess, as Kraus<sup>52</sup> has shown, a hypoplastic pituitary, so that the response of the latter is not as marked as those possessing a normal or hyperplastic pituitary It is to be emphasized, however, that there is, on the whole, some pituitary response to primary suprarenal deficiency even though the pituitary is hypoplastic

In normal dogs possessing a normal pituitary, if one produces an acute adrenal insufficiency by bilateral adrenalectomy the pituitary is able to respond by hyperplasia, and polycythemia results

Clinically, at least, the general rule is that primary suprarenal insufficiency is accompanied by pituitary insufficiency It reverts, there-

46 Smith, P E Disabilities Caused by Hypophysectomy and Their Repair, Tuberal (Hypothalamic) Syndrome in the Rat, *J A M A* **88** 158 (Jan 5) 1927

47 Evans, H Harvey Lectures, Philadelphia, J B Lippincott Company, 1923-1924

48 Putnam, T J, Benedict, E B, and Teel, H M Studies in Acromegaly, *Arch Surg* **18** 774 (April) 1929

49 Hofstatter, R Ueber Befunde bei hyperhypophysierten Tieren, *Monatsschr f Geburtsh u Gynak* **19** 387, 1919

50 Houssay, B Estudios sobre la accion de los extractos hipofisianos Ensayos sobre la fisiologia de lobulo posterior de la hipofisis, Buenos Aires, A Guidi Buffarini, 1911

51 Moehlig, R C, and Osius, E The Pituitary Factor in Arteriosclerosis, *Ann Int Med* **4** 578, 1930

52 Kraus, E J, and Traube, O Ueber die Bedeutung der basophilen Zellen der menschlichen Hypophyse, *Virchows Arch f path Anat* **268** 315, 1928 Kraus, E Zur Pathologie des Morbus addisonii (Befunde in Hypophyse und Nebennieren), *Beitr z path Anat u z allg Path* **78** 283, 1927

fore, to the constitutional make-up of the patient, in that he either does or does not congenitally possess an active pituitary gland

Substantial proof of this is offered by the work of Kraus and his associates. Kraus and Traube<sup>52</sup> examined two hundred and thirty-two pituitaries of persons who had been ill but a short time, so that no change in the pituitary would be expected from the illness. Another group was obtained from persons who had either died by accident or had committed suicide. The conclusions arrived at were as follows:

1 The most important findings in our systematic examination of two hundred and thirty-two cases in which the basophil cells were studied give the following results. Normal people of medium build (mesosthenic habitus), normal development and nutrition show, on the whole, a constant number of basophil cells in the anterior lobe, which we designate in our work as X X X.

2 Normal persons of hypersthenic habitus show, as a rule, a marked increase of the basophil cells as compared with those of the healthy mesosthenic habitus.

3 Persons with diseases which attack, as a rule, the hypersthenic type, such as essential hypertension, vascular sclerosis, contracted kidneys, constitutional obesity and, in a certain degree, chronic alcoholism, progressive paralysis and aortitis of syphilitic origin, show a very high percentage of basophil cells and a marked increase of the basophil cells as compared with the mesosthenic type.

4 Persons with high blood pressure, chronic nephritis and so-called secondary contracted kidneys also have a marked increase of the basophil cells as compared with the normal mesosthenic type.

5 Asthenic persons, such as the diabetic and tuberculous types, in whom the blood pressure is low show a diminution of the basophil cells in a majority of cases. Persons with cancer cachexia who have hypotension show a diminution of the basophil cells.

6 Persons with disturbances of the suprarenals or with marked hypoplasia or atrophic suprarenals, particularly of the Addisonian type, show in the majority of cases a distinct diminution of the basophil cells.

7 As to the relationship between the basophil cells of the pituitary and the suprarenals, 72.7 per cent of the persons with suprarenals rich in lipid (12 Gm or more) show a marked increase of the basophil cells.

8 Our studies on these two hundred and thirty-two pituitaries taken from normal and sick persons permit the conclusion that there is a definite relationship between the basophil cells of the pituitary and the constitutional type of the patient, likewise between these and the blood pressure as well as the state of the suprarenals. In other words, there is a definite relationship between the basophil cells, the constitutional make-up of the patient, the blood pressure and the size of the suprarenals.

9 There is, apparently, also a relationship between the basophil cells of the pituitary, the cholesterol content of the blood and the suprarenals. This is important because of the relationship between the cholesterol content of the blood and vascular disturbances.

10 Concerning the relationship between the number of the basophil cells of the pituitary and changes in the thyroid, thymus and sex glands, particularly the ovaries, we may not draw any definite conclusions.

We see, therefore, that the state of the pituitary is reflected in the suprarenal cortex. The constitutional type of the patient, the size of the suprarenal cortex, the blood cholesterol value and the number of pituitary basophils parallel one another.

As further confirmation of Kraus' work, Mjassnikow<sup>53</sup> found that hypersthenic persons have a blood cholesterol value of 1.8, whereas those of the asthenic type show a definite decrease, the cholesterol value being 1.3. Kraus believes, therefore, that there is a definite parallelism between the cholesterol content of the blood and the basophil cells.

Without entering into a consideration of hypertension, it is interesting that the syndrome described by Cushing usually includes hypertension. The relationship between the cholesterol metabolism, suprarenal cortex, hypertension and pituitary basophils is important. Berblinger<sup>54</sup> found that the basophil cells extend into the posterior lobe, from which comes the blood pressure-raising principle.

Moehlig and Osius<sup>51</sup> fed rabbits for one hundred days on a diet of high cholesterol content and injected daily doses of posterior lobe extract, this produced, among other things, an intense arteriosclerosis and marked hyperplasia of the adrenal cortex. It is possible that the basophil cells of the anterior lobe may furnish the "mother" substance to the posterior lobe, as would be suspected from Berblinger's histologic studies.

Zondek<sup>55</sup> expressed the opinion that this is the reason why posterior lobe extract at times produces the same results and reactions as his anterior lobe substance.

Klaus<sup>52</sup> reported on the changes in the pituitary in four cases of Addison's disease. Three of the four cases showed regressive changes in the basophil cells of the pituitary, whereas in the fourth case no particular change was found in this gland. In the three cases with changes, the basophil cells showed a varying degree of granulation loss, massing together of the cells and a marked diminution in the number of cells.

Of six additional cases of suprarenal atrophy, four showed typical Addison's disease. In another case of Addison's disease the basophil cells were diminished to a slight degree, showing a weak granulation and no great changes. In those cases in which the pituitary does not regenerate, there follows atrophy of the cells with thinning of the connective tissue, if regeneration does set in, either a new formation of chief cells or small chromophobe cells ensues or there may be some granulation of

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<sup>53</sup> Mjassnikow, A. L. Beiträge zur Konstitutionsforschung, Blutcholesteringehalt und Konstitution, *Ztschr f klin Med* **105** 228, 1927.

<sup>54</sup> Berblinger, W., in Henke and Lubarsch. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 8.

<sup>55</sup> Zondek, B. *Arch f Gynak* **144** 491 (Oct.) 1931.

the basophils with deeper staining qualities. Rarely do there follow full-fledged basophil cells.

Kiyono<sup>56</sup> reported two cases of Addison's disease. The first patient had tuberculosis of the suprarenals and the pituitary was small, the anterior lobe was hyperemic, the basophils were reduced and diminished pigment was present in the posterior lobe. The second case was associated with otitis media. The weight of the pituitary was 0.5 Gm. The anterior lobe was hyperemic, the eosinophils were not lessened and stained deeply, a colloid cyst was present in the pars intermedia and the posterior lobe contained no pigment.

Berblinger<sup>57</sup> cited a case of Addison's disease in a 7 year old boy with a high grade suprarenal hypoplasia in which the pituitary showed no characteristic changes. His other case of Addison's disease was due to a caseous degeneration of the suprarenals, and the pituitary showed a lessening of the chromophils. He gave as his opinion that this represents suprarenal insufficiency only and not a complete *Organ Ausfall*, and therefore this will influence the extent of the pituitary reaction. Whether, Berblinger said, the basophils deliver a different secretion than the eosinophils is as yet unsettled.

Harrop and Weinstein<sup>58</sup> reported a case of Addison's disease in which hypoplasia of the basophils of the anterior lobe was found.

We observed the following case:

S. B., a white man, aged 51, an American, entered Harper Hospital on Jan. 19, 1932, complaining of loss of weight and strength, gastric disturbances, pain and swelling of the right knee and easy fatigue for about two years.

In October, 1927, while in good health, he began to have a constant dull aching pain and soreness in the right flank which developed suddenly, independent of trauma or other symptoms. It continued without radiation and without urinary disturbances up to the time of admission, but in a milder form. In April, 1930, trauma to the right knee resulted in a painful reddened swelling which has persisted with exacerbations up to the present time. It remained swollen and tender and developed a brawny color. In January, 1931, he noticed he was losing weight and strength. In October, 1930, he weighed 245 pounds (111.1 Kg.), and in June, 1931, nine months later, he weighed only 137 pounds (62.1 Kg.). By April, 1931, the weakness and fatigability had become so marked he had to give up all activity. In June a severe gastric upset with nausea and vomiting, but without jaundice, caused his physician to prescribe for liver trouble, and on this regimen he remained fairly comfortable until November 1. During this period a yellowish tint to the skin developed, and brownish pigmented spots appeared on the skin of the abdomen, chest, face and arms. After November, the patient began

56 Kiyono, H. Histopathologie der Hypophyse, Virchows Arch f. path. Anat. **259** 388, 1926.

57 Berblinger, W. Die korrelativen Veränderungen an der Hypophyse des Menschen, Klin. Wchnschr. **7** 9 (Jan. 1) 1928.

58 Harrop, G. A., and Weinstein, A. Addison's Disease Treated with Suprarenal Cortical Hormone (Swingle-Pfiffner), J. A. M. A. **98** 1525 (April 30) 1932.

to lose more weight and strength, his knee gave him much discomfort and he had several severe attacks of vomiting

There was never any blood in the vomitus or any bloody or tarry stools. No history of alcoholism was obtained. The only past illness was malaria in 1908. At the age of 20, following an injury while working in a coal mine, he had gross hematuria for a week.

His father died of pneumonia, his mother, six brothers and three sisters were living and well. Two brothers died in infancy, and one was killed in an accident. Two sisters died of acute infectious disease. There was no family history of tuberculosis.

The patient had been married twenty-nine years. His wife and two children were living and well, three children died in infancy of intestinal disease.

Examination disclosed a well developed but poorly nourished man of 51 years, alert and cooperative. The skin of the face and neck was plethoric and showed a brownish discoloration over the chest, arms and abdomen. The mucous membrane of the mouth under both upper and lower plates was pigmented. The heart sounds were distant. The heart was of normal size. The blood pressure was 122 systolic and 80 diastolic, the pulse rate was 78. The peripheral arteries were compressed with difficulty. Diminished breath sounds only were found in the lungs, resonance being unimpaired. The right knee was swollen, reddish brown and tender. Active and passive movements were painful and flexion greatly limited. There was moderate tenderness deep in the right flank. The liver and spleen were just palpable. The urine was normal. The hemoglobin content was 94 per cent. The red blood cells numbered 6,510,000, the white blood cells, 9,100. The differential count showed polymorphonuclears, 52 per cent, small lymphocytes, 34, large lymphocytes, 10, and eosinophils, 4. Subsequent counts were essentially the same.

Roentgen examination disclosed a destructive process in the right knee joint, probably tuberculous, and a bilateral parenchymal involvement of the upper lobe, with a lobular distribution of tuberculous origin. After examining the skull the roentgen department reported: "There is slight depression of the floor of the sella, which would indicate some pituitary enlargement. There is no evidence of erosion of either the anterior or the posterior clinoids. The pineal gland shows calcification, which is normal for adult life."

The urine showed no sugar at any examination. Tests for dextrose and levulose tolerance and the bromsulphalein tests gave results within normal limits.

The diagnosis was Addison's disease, tuberculosis of the right knee joint and polycythemia.

The patient's course in the hospital was definitely downward, with severe gastro-intestinal upsets, lowered blood pressure and finally coma and death, fourteen days after admission. Permission for postmortem examination could not be obtained, but we may safely assume that there was a destruction of the suprarenal glands by a tuberculous process.

We believe that this man originally possessed a very active pituitary gland and was able to respond with a polycythemia and marked pigmentation.

Bell<sup>59</sup> reported a case which he diagnosed as Addison's disease associated with acromegaly. Unfortunately no autopsy was performed,

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<sup>59</sup> Bell, B. The Pituitary, New York, William Wood & Company, 1919.

this would have been enlightening for several reasons. Hyperplasia of the pituitary is usually associated with hyperplasia of the supra-renal cortex. This case of Bell's is unusual, therefore, unless we postulate a primary hypoplasia of the supra-renal cortex with secondary hyperplasia of the pituitary gland.

The state of the pituitary after extirpation of the adrenals in animals has been reported on by few workers. Boinet<sup>60</sup> and Marengli<sup>60</sup> found hyperfunction of the pituitary after extirpation of the adrenals. Bell<sup>59</sup> found hypertrophy of the middle lobe, whereas Alquier<sup>60</sup> and Pende<sup>60</sup> found no changes. Urechia and Mihalescu<sup>61</sup> found enlargement and congestion of the anterior pituitary and a definite increase of the eosinophils. Boyd<sup>62</sup> said that removal of most of the adrenal tissue is followed by pituitary hyperplasia.

Poos,<sup>63</sup> using various animals in a large series of experiments, concluded that the pituitary always reacts qualitatively in the same way when other glands of internal secretion are disturbed by experimental attack. The quantitative differences are dependent on the severity of the endocrine changes produced and, secondarily, on the length of the experiment. He differentiated four stages of reaction processes affecting the pituitary after adrenalectomy: (1) the stage of increased physiologic reaction, (2) the stage of pituitary hydrops, (3) the stage of degeneration and (4) the stage of pigment formation.

He expressed the opinion that the pituitary is influenced by general metabolic disturbances and that this metabolic stimulus always results in a qualitative change in this gland. The quantitative change, he said, is dependent on the severity of the endocrine changes produced and, secondarily, on the length of the experiment.

Lehmann's<sup>64</sup> experiments on rats concerned the reaction of the pituitary after ablation of the adrenals. Soon after extirpation of both adrenals, the hair became brittle, even in the young animals, and finally fell out, particularly in the region of the back. In some animals, black hair became lighter and there was some lessening of the epidermal pigment. The adenohypophysis showed a diminution of eosinophils. The

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60 Quoted by Bayer, G., in Hirsch, M. *Handbuch der inneren Sekretion*, Leipzig, Curt Kabitzsch, 1928, vol 2, pt 3, p 752.

61 Urechia, C. I., and Mihalescu, S. *Histologic Study of Tuber Cinereum and Nuclei of Base in Acute Operative Insufficiency of Suprarenals*, *Rev. franç. d'endocrinol.* **3** 296 (Oct.) 1925.

62 Boyd, W. *The Pathology of Internal Diseases*, Philadelphia, Lea & Febiger, 1931.

63 Poos, F. *Genese und Deutung der Reaktionsformen der Hypophysis cerebri*, *Ztschr. f. d. ges. exper. Med.* **54** 709, 1927.

64 Lehmann, J. *Die Struktur des Hirnanhangs nebnierenloser Ratten*, *Ztschr. f. d. ges. exper. Med.* **65** 129, 1929.

pars intermedia did not show any particular change. The pars nervosa showed a high grade edema, particularly at the base of the posterior lobe. Lehmann found that the pigment disappeared rapidly in the pars intermedia and never returned.

Berblinger<sup>57</sup> took exception to some of Poos' conclusions. He expressed the belief that the nature and reactions of glandular secretions are specific and are not really due to a general metabolic change. Furthermore, Berblinger said that if one studies the reactions of the pituitary of the human subject, not only in pregnancy but in athyreosis and hypothyroidism, he will find quantitative differences. As illustrative of the latter reaction he considered hypertrophy of the chief cells of the pituitary in cancer with hepatic metastasis, also in two cases of multiple myeloma. However, these pituitary changes do not occur constantly in cases of neoplasm other than in association with athyreosis or hypothyroidism.

Concerning the production of the Cushing syndrome due to pituitary basophilism and also pituitary disturbances in general, a logical explanation is found in the embryohormonic relations of the pituitary to mesodermal tissues. This relationship was shown originally by one of us (Dr Moehlig<sup>65</sup>) in 1914, and since then the principle outlined has gained some acceptance (Cushing and Davidoff,<sup>66</sup> Putnam,<sup>67</sup> Brugsch<sup>68</sup> and Hofbauer<sup>69</sup>).

For cleanness, the mesodermal tissues are given as follows:

- 1 Connective tissue (all types of connective and supporting tissues)
- 2 Cutis or corium, including the hair papillae
- 3 Cartilage, bone
- 4 Dentin and cementum of the teeth
- 5 Pigment cells, mesodermal
- 6 Lymph glands, lymphatics, lymph cells
- 7 Spleen
- 8 Blood
- 9 Blood vessels
- 10 Fat cells

} Reticulo-endothelial  
system

<sup>65</sup> Moehlig, R. C. A Study of the Ductless Glands, Detroit M. J. **14** 268, 1914.

<sup>66</sup> Cushing, H., and Davidoff, L. Studies in Acromegaly. V. The Pathological Findings in Four Autopsied Cases of Acromegaly with a Discussion of Their Significance, New York, Rockefeller Institute for Medical Research, 1927, monograph no. 22.

<sup>67</sup> Putnam, T. Separation of Growth-Producing Hormone from That Inducing Premature Estrus in the Anterior Pituitary Gland, Arch. Surg. **18** 765 (April) 1929.

<sup>68</sup> Brugsch, T. Lehrbuch der inneren Medizin, Berlin, Urban & Schwarzenberg, 1930, vol. 1, p. 141.

<sup>69</sup> Hofbauer, J. Ueber Beziehungen des Hypophysenvorderlappens zum Uteruscarcinom, Klin. Wchnschr. **9** 2153 (Nov. 14) 1930.

- 11 Smooth muscle (with exception of the iris musculature)
- 12 Renal cells
- 13 Nerve and corpuscles
- 14 Joint cavities, bursae, subarachnoid and subdural spaces and their linings
- 15 Suprarenal cortex
  - (a) Pleurae, peritoneum and pericardium
  - (b) Sex glands and tissues
  - (c) Skeletal muscle, including the specialized cardiac muscle

} Mesothelium

The suprarenal cortex controls the mesothelial tissues cited. This embryohormonic relationship has been discussed elsewhere<sup>70</sup>. It is apparent that the pituitary could influence and control these tissues as well.

Cushing<sup>1</sup> said

While there is every reason to concede, therefore, that a disorder of somewhat similar aspect may occur in association with pineal, with gonadal or with adrenal tumors, the fact that the peculiar polyglandular syndrome, which pains have been taken herein conservatively to describe, may accompany a basophil adenoma in the absence of any apparent alteration in the adrenal cortex other than a possible secondary hyperplasia, will give pathologists reason in the future more carefully to scrutinize the anterior pituitary for lesions of similar composition.

It is our opinion, however, that the majority of symptoms characterizing this syndrome are always due to involvement, either primarily or secondarily of the pituitary, regardless of which endocrine gland is primarily involved.

From the metabolic standpoint it is certain that hyperglycemia with glycosuria is frequently found in pituitary disturbances. Houssay<sup>71</sup> and his associates have contributed much to our knowledge on the importance of the pituitary in carbohydrate metabolism. They believe that the pituitary is the most important regulating factor in carbohydrate metabolism. From this we can also infer that the hypoglycemia usually present in atrophic conditions of the suprarenal cortex, such as seen in Addison's disease, is really due to *failure of the pituitary function*.

70 Moehlig, R. C. (a) Ductless Gland Cell Control, Monograph (privately printed), 1918, (b) Selective Action of the Suprarenal Cortex on Mesothelial Tissues, *Am J M Sc* **168** 553, 1924, (c) Embryohormonic Relations of the Suprarenal Cortex to Mesothelial Tissues, *Ann Int Med* **1** 828, 1928, (d) *J Lab & Clin Med* **16** 118, 1930, (e) footnote 45, (f) footnote 65, (g) Moehlig, R. C., and Ainslee, H. B. Pituitary Gland and Cholesterol Metabolism, *Ann Clin Med* **5** 772, 1927, (h) Posterior Pituitary Extract and Cholesterol Metabolism, *Am J Physiol* **80** 649, 1927.

71 Houssay, B. A. Die funktionellen Beziehungen zwischen der Hypophyse und dem Pankreas, *Endokrinologie* **5** 103, 1929. Houssay, B., and Biasotti, A. Pankreasdiabetes und Hypophyse beim Hund, *Arch f d ges Physiol* **227**.664, 1931. Hypophysektomie und Pankreasdiabetes bei der Krote, *ibid* **227** 239, 1931.



and not to the suprarenal cortex <sup>71a</sup> This is well illustrated in pituitary cachexia in which hypoglycemia is pronounced

Then too, the influence which this gland has on cholesterol metabolism by affecting the mesodermal fat cells and suprarenal cortex is gaining recognition and accounts for the hypercholesteremia

Klaus,<sup>52</sup> Smith<sup>72</sup> Raab,<sup>73</sup> Anselmino and Hofmann,<sup>74</sup> Mjassnikov<sup>53</sup> and Moehlig and Ainslee<sup>70g,h</sup> have shown the influence which the pituitary has on fat metabolism

Disturbances of cholesterol are associated with hypertension, diabetes mellitus, nephritis arteriosclerosis and several other conditions

In the article by Moehlig and Ainslee,<sup>70a</sup> some of the points made are of interest in regard to the syndrome under discussion They said "Furthermore, the pituitary supposedly has an erythropoietic function In hyperpituitarism, polycythemia with an increased blood volume is present and in hypopituitarism, anemia with a lessened blood volume is present" Part of the summary was "The pituitary gland, regulating the suprarenal cortex and other mesodermal tissues, plays an important rôle in the pathogenesis of diseases associated with abnormalities of cholesterol metabolism Such diverse clinical entities as arteriosclerosis hypertension, certain types of nephritis disturbances in the volume of blood cholelithiasis diabetes and uterine fibroids are found to have important relations to states of pituitary hyperfunction and exhaustion"

The hypertrichosis is a pituitary and not a suprarenal symptom As noted, the hair papilla with its nutritional element is a mesodermal tissue so that the pituitary overactivity results in stimulation of the hair papillae Persons with hypersthenic, acromegalic, pituitary, basophilic and hyperpituitary states in general have marked hirsutism The recent work of Bengtson<sup>75</sup> as well as that of earlier workers,<sup>76</sup> has shown the influence of the pituitary on the growth of the hair Hypophysectomy in dogs results in permanent lanugo formation<sup>76</sup>

The hypertrichosis of persons with ovarian tumors is also, we believe of pituitary origin

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71a This should be qualified in that the suprarenal cortex influences the skeletal muscle metabolism

72 Smith, P E Disorders Induced by Injury to the Pituitary and the Hypothalamus, *J Nerv & Ment Dis* **74** 56, 1931

73 Raab, W Role of Pituitary Posterior Hormone in Fat Metabolism *Endocrinology* **14** 385 (Nov-Dec) 1930

74 Anselmino, K J, and Hofmann, F Fat Metabolism Hormone of Anterior Lobe of Hypophysis, *Klin Wchnschr* **10** 2380 (Dec 26) 1931

75 Bengtson, B Pituitary Therapy of Alopecia, *J A M A* **97** 1355 (Nov 7) 1931

76 Aschner, B, in Hirsch, M *Handbuch der inneren Sekretion*, Leipzig, Curt Kabitzsch, 1928 vol 2, p 354

Briefly, the development of the hair is always a result of pituitary activity, regardless of which endocrine gland is involved

This specific influence of the pituitary on mesodermal tissues provides a much better understanding of the hypertrichosis seen in supra-renal and ovarian disturbances, which is due to secondary involvement of the pituitary

Polycythemia is, no doubt, the result of the pituitary influence on the mesodermal reticulo-endothelial system. If we study the influence of the pituitary on growth, it is reasonable to assume that the important hematopoietic system should be stimulated to activity by its secretion. The mesodermal bone tissue, spleen, reticulo-endothelial system of the liver, etc., are known to be influenced by the state of the pituitary. It is well known that in hyperpituitary states, such as that seen in pituitary eosinophilism or acromegaly, the whole hematopoietic system becomes hyperplastic. The relationship of the pituitary to cholesterol metabolism, previously discussed, is of importance in regard to the protective influence of cholesterol on erythrocytes.

The pigmentation which so often accompanies hyperpituitary conditions may be due to the influence of the pituitary on the mesodermal pigment cells. We cannot, of course, here consider the vast field of pigmentation, but if pigment formation is a metabolic phenomenon, the mesodermal origin of all pigment is most likely. Such an assumption would give the pituitary a major rôle in pigmentation. What we would like to suggest is that the pituitary is concerned in the production of Addisonian pigmentation. At present we have been bound by convention to believe that the suprarenals are the only responsible factors.

Certain clinicopathologic data are of great importance in this discussion.

1. Hyperpituitary conditions, such as acromegaly and basophilism, are usually found in dark-haired, dark-complexioned, hypertrichotic persons.

2. Hyperfunctioning suprarenal cortex tumors are also found in this same type and, as our cases suggest, the pituitary becomes hyperplastic in these conditions.

3. In pituitary cachexia (Simmond's disease), representing an extensive degree of pituitary atrophy or destruction there is present a hypoplasia of the suprarenal cortex of a degree comparable with that seen in Addison's disease yet we find no pigmentation. The patients have asthemia and a low blood pressure, which is also comparable with that seen in Addison's disease. In our case, in a girl of 15 years, pituitary cachexia developed with marked decay of the teeth, falling out of the hair, amenorrhea, a loss of 102 pounds (46.2 Kg.) in nine

months, a blood pressure of 74 systolic and 60 diastolic and extreme asthenia. The patient was light in color and showed no pigmentation, owing, we believe, to the fact that the pituitary was primarily at fault. It is logical to assume that in these cases, in which the pituitary is primarily hypoplastic, it cannot respond to atrophy of the suprarenal cortex (which it causes) as in primary disease of the suprarenal cortex.

The amenorrhea, due, as has been shown, to atrophic and fibrotic ovaries, needs mention. This would seem to be an end-result of pituitary overactivity, in that the ripening mulberry stage has been followed by fibrosis and atrophy. It would be interesting to see the ovaries in an early stage of pituitary basophilism. Experimentally, as we know from Zondek's<sup>77</sup> work, hormonal sterilization may be produced by injections of anterior lobe substance. The whole ovary becomes a mass of corpus luteum and amenorrhea results. It would seem that the fibrotic and atrophic ovary is the late result of this lutein stage. Clinically, we have seen comparatively young women of the dark-complexioned, hypertrichotic type, who give a history of menstruation beginning early in life (from 10 to 11 years of age), rather profuse and lasting from seven to ten days, this is followed in a few years by too frequent menstruation (twice a month) and, within a short time, by irregularity, skipping one or two months, finally there is complete amenorrhea.

We feel that this type duplicates the different stages of ovarian cellular activity in response to pituitary overactivity.

Our endeavor to show that the pituitary is really responsible for many signs and symptoms erroneously ascribed to the suprarenal cortex might lead one to believe that the function of the latter is a minor one. On the contrary, we feel that the suprarenal cortex, essential as it is to life, has definite relations to the mesothelial portion of the mesoderm. Its secretion is essential for the proper development and functioning of these tissues. This was emphasized in other papers.<sup>70</sup>

#### REPORT OF CASES

CASE 1—Mrs. S., a housewife, 43 years old, entered Harper Hospital on June 11, 1931, complaining of nervousness and palpitation of the heart for eight years, multiple ecchymoses for four years, flushing of the face and intermittent pains in the joints for one year.

Her father was killed in an accident at the age of 70, but her mother is living and well at the age of 65. Both were short and stout, the mother being of the same build as the daughter, 5 feet (152.4 cm) tall and weighing 138 pounds (62.6 Kg). She is married and had one pregnancy terminating spontaneously at six months. Her menses began at the age of 14 years and were regular but too profuse. She did not menstruate after an operation for the removal of tumors of the womb nine years before the present examination, she thought that her

<sup>77</sup> Zondek, B. *Die Hormone des Ovariums und des Hypophysenvorderlappens*, Berlin, Julius Springer, 1931.

ovaries were also removed at that time. Her tonsils were removed eleven years before. Four years before examination she had two operations on the sinuses, and in the same year bladder gravel was removed. All the teeth were extracted 3 years before. She has had no serious illnesses.

She was well for about a year following the removal of the fibroids and ovaries, and then (eight years before examination) she noticed the onset of nervousness, irritability and emotional outbursts. Associated with this were occasional periods of giddiness and palpitation, at times severe, which were ushered in without cause. This situation continued without change until about four years before, at which time she noticed huge ecchymoses making their appearance at irregular intervals, apparently without cause. The ecchymoses cleared readily and then appeared elsewhere, a brownish pigmentation remaining. About two or three years before, she noticed bright blood oozing from the skin at times, without finding any apparent bleeding point. At one time she bled from the forehead and again from the fingers. The bleeding always stopped spontaneously.



Fig 1 (case 1) —Note the masculine appearance, marked hirsutism and prominent eyes

Cuts and bruises, however, always healed normally. About one year before, she began to notice a peculiar flushing of the face accompanied by severe headaches of a throbbing character, especially over the left frontal and temporal areas. At these times, she said, her blood pressure was found to be as high as 230 systolic. Associated symptoms were dizziness, blurring of vision and the appearance of yellow spots before the eyes. About this time her skin became very dry, although she occasionally perspired, and she noticed an excessive growth of hair over the face and other parts of the body. Then fleeting multiple pains in the joints became troublesome, all the joints being involved at one time or another, although there was never any redness or swelling. During the later months, a peculiar crawling sensation gradually developed in the skin of the arms, then in the scalp and later all over the body. The patient's weight remained normal all through the illness, although weakness and fatigue became part of the picture.

To be noted on examination were the masculine facies, the plethoric appearance of the face, the prominent eyes, a beard, a goiter, a heart enlarged to the left, a blood pressure of 170 systolic and 104 diastolic, numerous striae cutis

distensae on the abdomen and thighs, hirsutism of the arms and legs and large brownish shiny pigmented areas over the thighs, chest and arms. The adiposity was largely confined to the trunk, the hands and feet being remarkably small relatively (fig 1)

The Wassermann reaction was negative, the urine normal, the blood calcium 9.98 mg, the blood sugar 0.200 per cent and the nonprotein nitrogen 27.3 mg. The basal metabolic rate was plus 31 three months before entry and minus 1 in

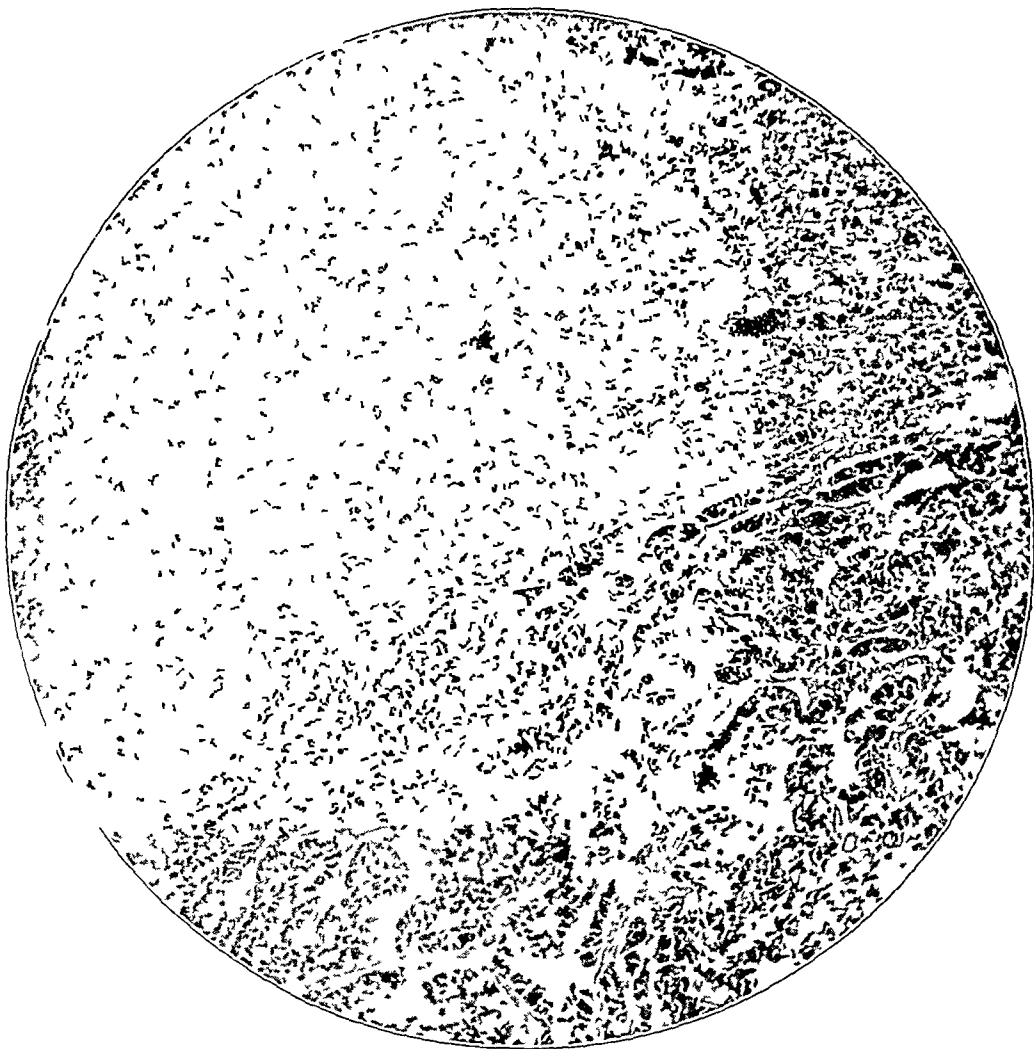


Fig 2 (case 1)—Section of tumor, showing a rapidly growing basophilic papillomatous adenoma

the hospital. Roentgen examination of the skull showed a normal sella turcica. Examination of the blood showed hemoglobin, 106 per cent, red blood cells, 6,640,000, and volume of red cells per hundred cubic centimeters of blood, 53, a value distinctly above the normal for women.

The symptoms of goiter were so marked that it was felt that the adenomatous gland should be removed, the polyglandular disturbance being evident. On June 15, a subtotal thyroidectomy was performed, two enlarged hard lobes being removed. About seven days after the operation a psychosis developed with mild

convulsive seizures, the temperature rose to 100.2 F., and the patient died, sixteen days after operation, with symptoms of myocardial failure.

The postmortem examination was, unfortunately, limited to the head and the report was as follows: "Brain surfaces and meninges showed no exudate or hemorrhage. The pituitary body was symmetrically enlarged (1.75 by 1 cm.) and on cut section shows a small circumscribed area of whitish-gray tissue about 2 cm. in diameter (adenoma). Microscopically there is a diffuse adenomatous

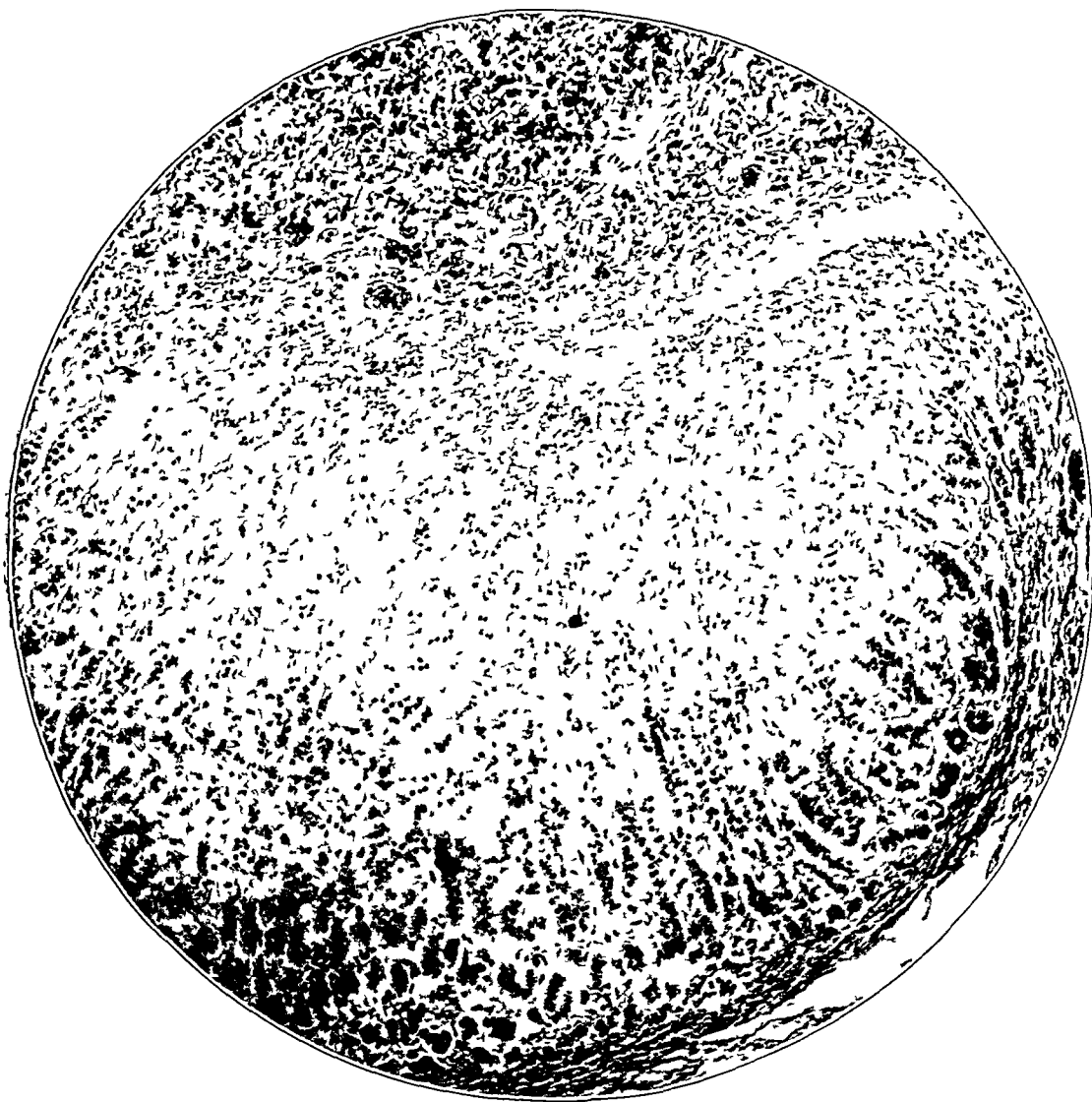


Fig. 3 (case 2)—Suprarenal cortex of uninvolved side, showing adenomatous hyperplasia.

hyperplasia of the pituitary body, including both the basophilic and eosinophilic elements. In one area of the anterior lobe there is a rapidly growing basophilic papillomatous neoplasm (fig. 2). The bone from the skull appears normal.

The following case represents an interesting association of a suprarenal tumor with hyperplasia of the hypophysis and a pronounced polycythemia.

CASE 2—Mr S, a married, white laborer of 63 years, entered Harper Hospital in January, 1931, for repair of a left inguinal hernia and excision of a hydrocele on the same side (an industrial compensation case)

The past history and family history were entirely inconsequential. The patient's father, mother and siblings were all of average height and weight. He had never had any serious illness, and presented himself in perfect health. The hernia and hydrocele were repaired and the patient was sent home.

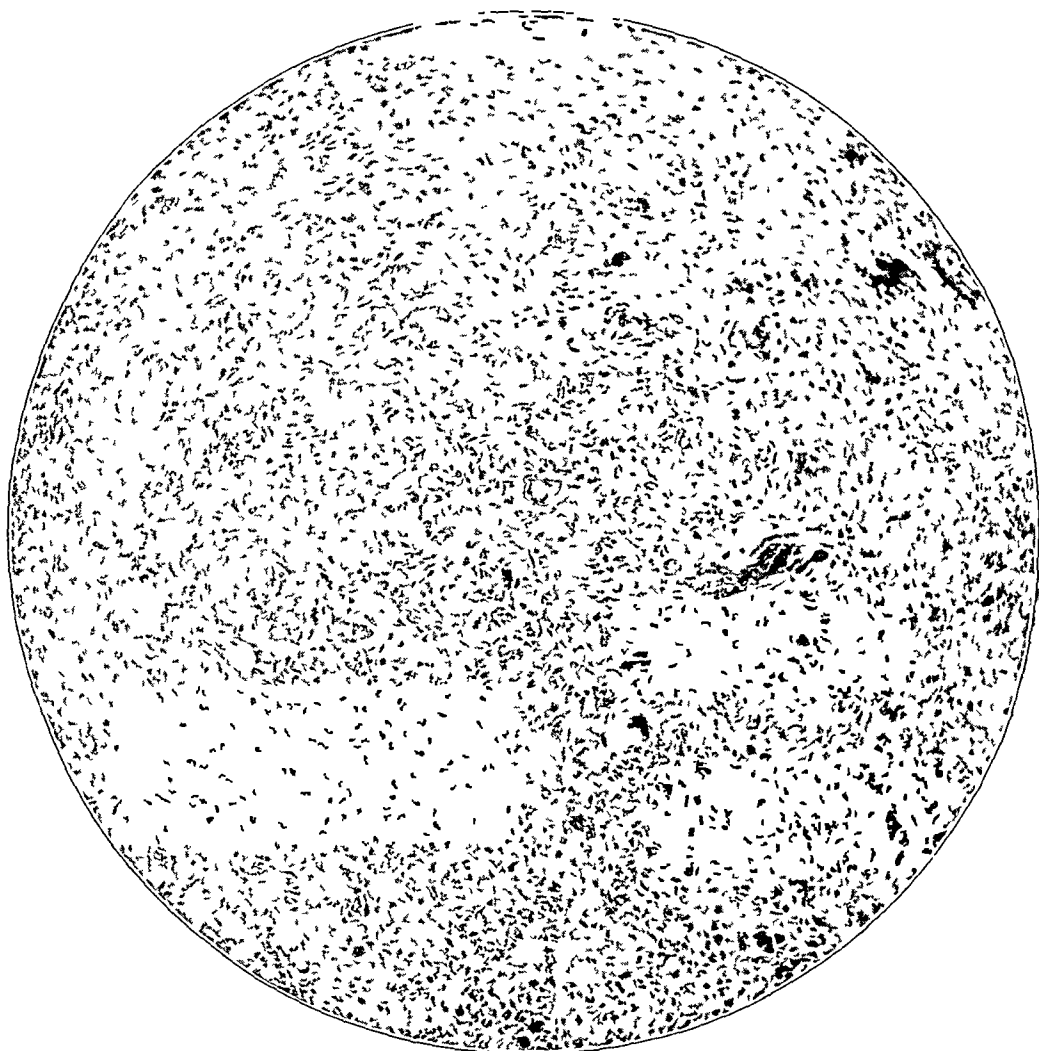


Fig. 4 (case 2)—Primary malignant neoplasm of the suprarenal cortex.

On February 15, he returned to the hospital complaining of vomiting and loss of weight. Examination disclosed a man in fair nutrition, not acutely ill. The only remarkable findings were a hard irregular mass, about 7 cm. in diameter, extending downward from the left costal margin and a smooth liver edge extending two finger breadths below the right costal margin.

Roentgen examination disclosed "evidence, we think, of pulmonary metastasis of a malignant neoplasm. Bilateral root deposit. Fluoroscopic evidence of enlarged liver and also questionably of the spleen. No indication of upper gastro-intestinal pathology. Cannot elicit definite evidence of malignancy in the lower bowel, although we could not exclude this condition."

The average values found in studies of the patient's blood may be summarized as follows: red blood cells, 8,194,000, hemoglobin, 153 per cent, reticulocytes, 13 per cent, polymorphonuclears, 95 per cent, lymphocytes, 5 per cent, and white blood cells, 8,000.

Over a period of fourteen days of observation no eosinophils or basophilic leukocytes were observed.

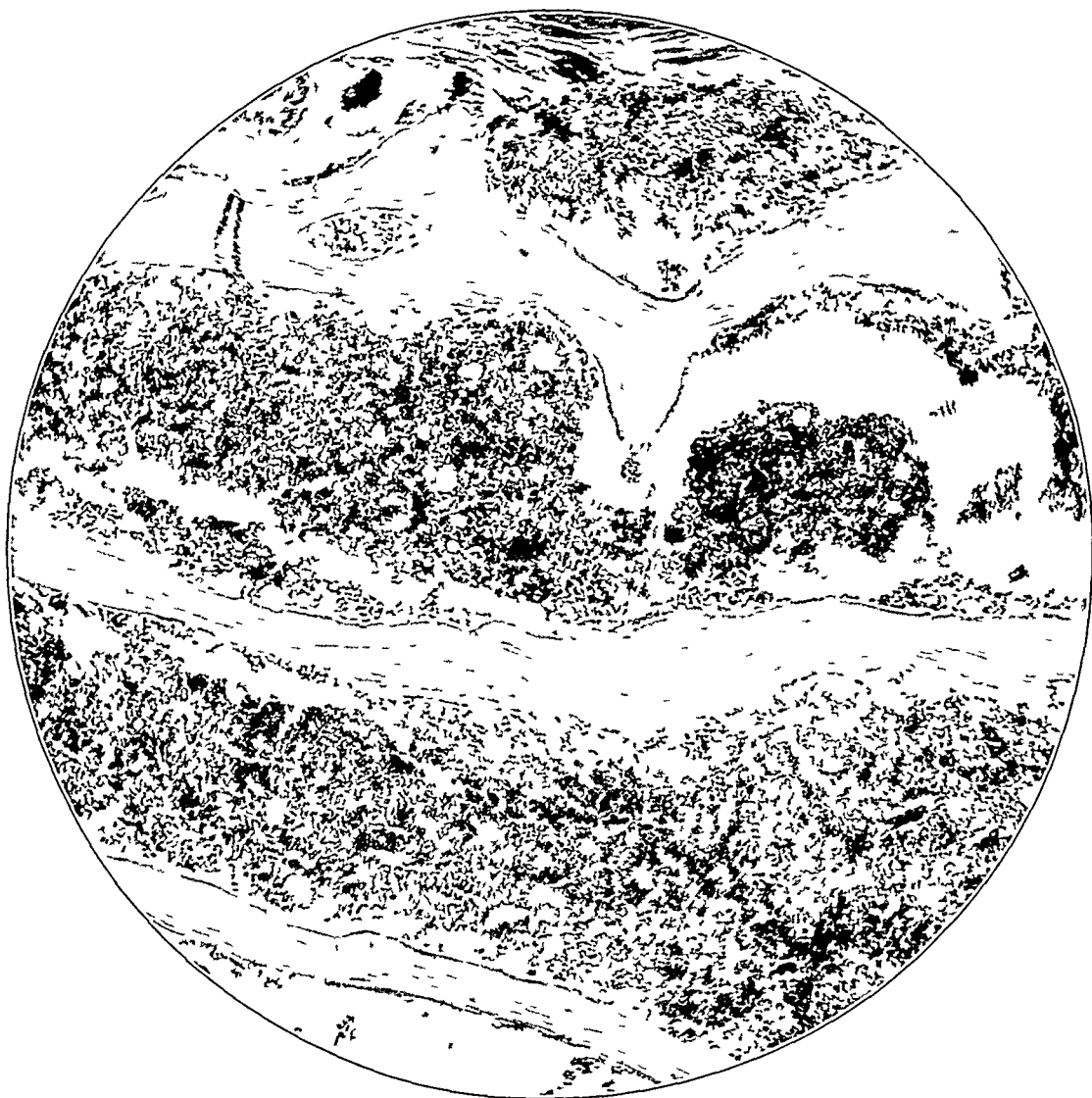


Fig. 5 (case 2)—Bone marrow, showing marked hyperplasia.

Urimysis and tests of levulose tolerance gave negative results. The nonprotein nitrogen amounted to 30 mg., the blood sugar to 0.095 per cent. The Wassermann test gave negative results, the test of liver function, results within normal limits.

At postmortem examination a large invasive tumor of the left kidney was found, which had metastasized to the lungs. Microscopically, this tumor "is a malignant angio-mesothelioma with large pale staining cells. The structure is different from the ordinary type of Grawitz tumor, and in some areas is markedly reminiscent of decidual tissue. In other areas the structure resembles the ordinary type of polymorphonuclear cell sarcoma with many division figures and pseudo-giant cells." The pituitary was not remarkable grossly but microscopically



showed "marked hypertrophy and hyperplasia of the basophilic elements" The bone marrow showed marked myeloid hyperplasia throughout the marrow space (figs 3 to 6, inclusive)

*Comment*—The first case was one of definite pituitary basophilism and duplicates those reported by Cushing<sup>1</sup> The neoplastic type of basophilism is an interesting feature of the pituitary picture The

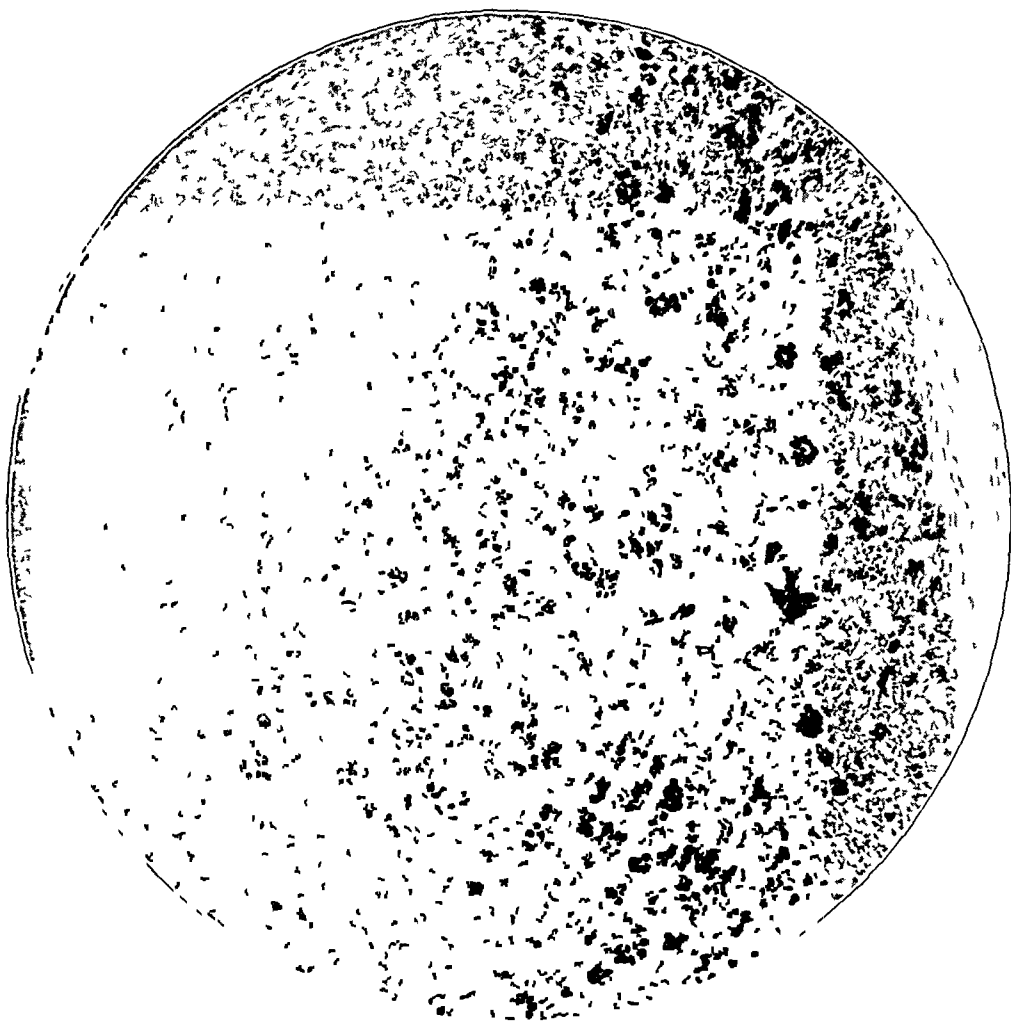


Fig 6 (case 2) —Pituitary, showing basophilism

polycythemia and spontaneous hemorrhages into the palms of the hands were striking features

The second case shows that a primary involvement of the suprarenal cortex results in a secondary response on the part of the pituitary in the nature of basophilism The polycythemia with a very high hemoglobin percentage was an outstanding feature

#### EXPERIMENTS

In order to test the validity of the assumption that ablation of the suprarenal cortex induces compensatory physiologic overactivity of the

pituitary gland, as indicated by changes in its histologic structure and by the appearance of polycythemia bilateral adrenalectomy was performed in eleven dogs and the blood picture observed. Only four dogs lived more than four days following operation, but in all cases an increase in the total number of circulating red cells was noted at the end of twenty-four hours, in the dogs that lived from four to six days this amounted to from 15 to 25 per cent, or an increase from the normal range of from 6,000,000 to 7,000,000 to over 8,000,000. In all save three the histologic picture of the pituitary gland changed within

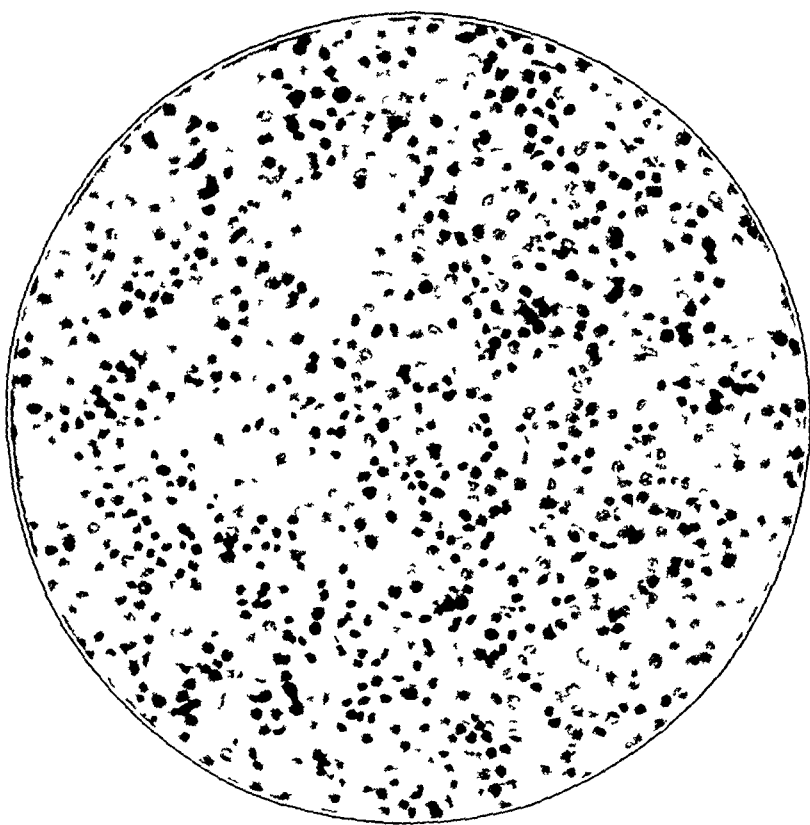


Fig 7—Pituitary of a dog (control)

twenty-four hours, to show a marked preponderance of basophils in contrast to the normal picture of almost complete eosinophilia. A series of ten pituitaries from normal dogs were studied to determine the normal histologic picture, which, as illustrated in figure 7, proved without exception to be a marked eosinophilia of the anterior lobe. In one case, however, an increase of 1,000,000 occurred in the red cell count and a marked eosinophilia was found in a microscopic study of the hypophysis, as shown in figure 8. In two other instances in which the period of survival was only twenty-four hours, no change in the normal eosinophilic picture was observed. The explanation of the eosinophilic picture in the former instance, in which a polycythemia was induced, is not clear. In every other instance a basophilic type of response was mani-

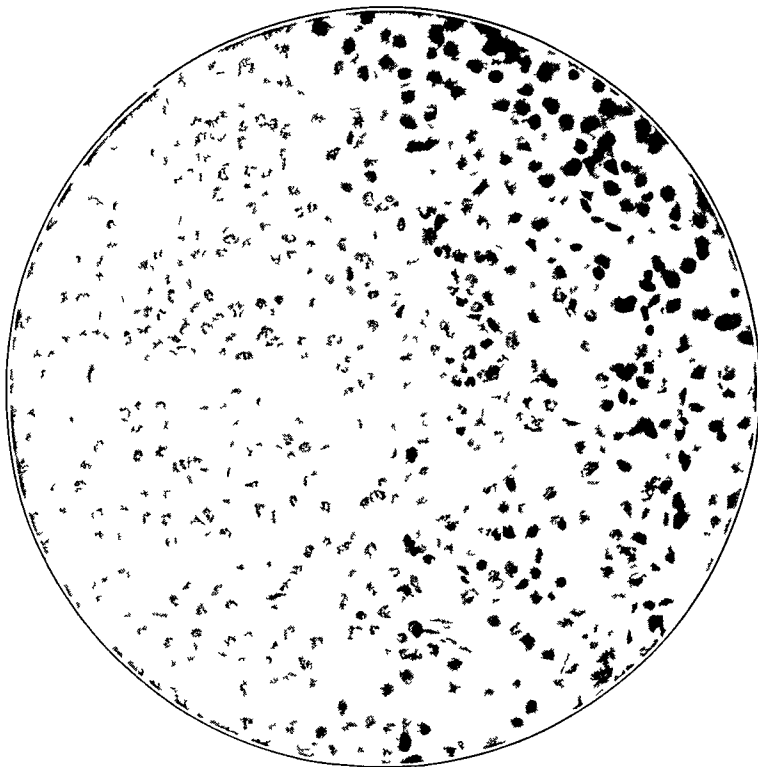


Fig 8—Pituitary of a dog, showing hyperplasia of the eosinophils

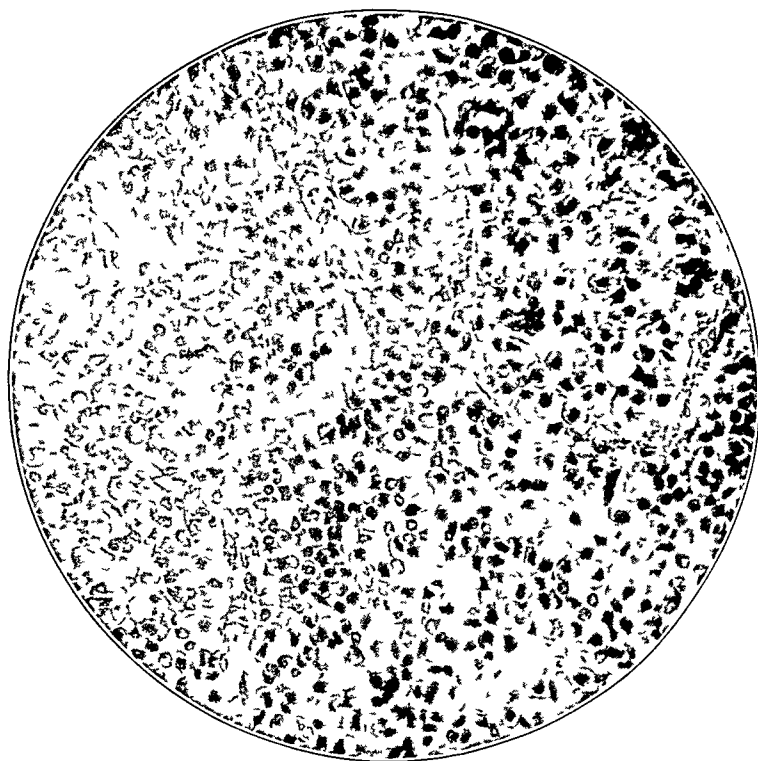


Fig 9—Pituitary of a dog, showing marked hyperplasia of the basophils twenty-four hours after adrenalectomy

tested by the pituitary, even in one dog that lived only twenty-four hours, a histologic study of the pituitary in this animal is well illustrated by figure 9

The reaction of one particular dog is noteworthy. A bilateral adrenalectomy was performed, and in forty-eight hours the red cell count had increased 15 per cent. Within four days the count had dropped to normal and the dog had completely recovered from the operation. An exploration was made, and a bean-sized remnant of adrenal gland was recovered, following which a polycythemia again

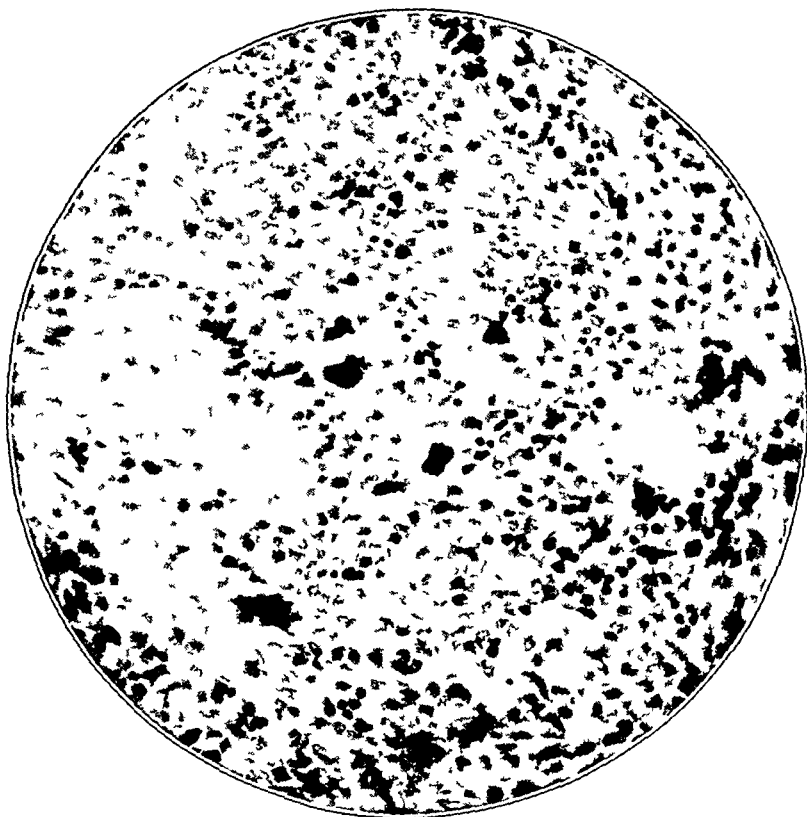


Fig 10—Myelosis of the spleen

appeared. His pituitary showed a marked basophilia and also a myelosis of the spleen as illustrated in figure 10, a reaction noted in only three instances, however.

Thus, in acute adrenal insufficiency in dogs, there was a marked basophilic response in the pituitary with an associated polycythemia and a less constant myeloid change in the spleen.

From our studies we were impressed with the fact that both eosinophilic and basophilic adenomas have some features in common. For instance, hypertension is found in both conditions, and hyperglycemia, or a tendency to it, is also common to both. Hypertichosis is a feature found in eosinophilism as well as basophilism. Polycythemia, as outlined in this paper, is likewise seen in both conditions, as is

kyphosis This would seem to indicate that the unitarian cell theory of Collin,<sup>78</sup> postulating that the chromophobe cell is the mother of all pituitary cells, has certain facts to prove it Be that as it may, the embryohormonic relation of the pituitary to the mesodermal tissues provides a logical explanation of the physiologic cell activity of this gland

While the problem of tumor formation is somewhat aside from the present consideration, it is readily seen that the application of this embryohormonic principle to neoplasms is a logical sequence of thought Certain clinico-pathologic observations strongly suggest that the pituitary-mesodermal relationship will prove to be of immense value in neoplasms of mesoblastic origin, particularly the sarcomas

The experiments on dogs open up some debatable points which need not concern us here It is realized that there are certain biologic differences between human beings and animals Dogs do not sweat like humans, but use the respiratory mechanism instead This may account for the increased number of red cells as compared with human beings Adrenalectomy, with its effect on the respiratory system by increasing its load, produces a rapid increase in red cells Experimental removal in animals does not, of course duplicate the gradual *Organ Ausfall* of human beings, but polycythemia is seen often enough in atrophy of the suprarenal cortex in man to indicate some points of similarity Then, too, the pathologic changes in the cells of the pituitary coming on so rapidly (in twenty-four hours) after extirpation of the adrenals lead one to believe that the chemical relationship between these glands (and, no doubt, between all endocrine glands) is a most intimate one

#### SUMMARY

Two cases of polycythemia vera with pituitary basophilism, coming to autopsy, are described One was a case of primary basophilic adenoma giving rise to the syndrome recently described by Cushing The other was a secondary basophilism in response to a suprarenal tumor

Experimentally induced polycythemia in dogs by bilateral adrenalectomy is also reported In these animals rapid and marked hyperplastic changes of the pituitary cells were found The hyperplasia was, in the majority of cases, confined to the basophil cells

We endeavored to show

- 1 The pituitary secretion has a very important influence on erythrocyte formation

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<sup>78</sup> Collin, R La neurocrinie hypophysaire Étude histophysiologique du complexe tubero-infundibulo-pituitaire, Paris, G Doin et Cie, 1928

2 Primary disease of the supraarenal cortex results in secondary pituitary changes, thus accounting for many signs and symptoms erroneously ascribed to the supraarenal cortex

3 The specific and selective embryohormonic relations of the pituitary gland to mesodermal tissues offer a reasonable explanation for the polymorphic signs and symptoms of pituitary disturbances

# INFECTIOUS POLYPOID COLITIS

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The colon is a relatively frequent site for multiple polyps of the mucosa with and without chronic ulceration. The true polyp is composed of hyperplastic glandular mucous membrane projecting into the lumen of the bowel. In the literature are recorded cases of so-called pseudopolyposis lymphatica,<sup>1</sup> in which the mucosal projections are caused by underlying hyperplastic lymph follicles, but no cited instance has been found simulating the case to be reported, in which nodular polypoid projections into the colon were caused by a peculiar granulation tissue composed mostly of large mononuclear cells filled with what appears to be a specific infectious micro-organism.<sup>2</sup> It has not been possible to cultivate the bacillus associated with the lesion, but it is hoped that a record of the case may lead to an earlier recognition of the disease, so that its bacteriology may be studied with care.

## REPORT OF A CASE

*History and Course*—W S, a 49 year old white truckman, entered the Vanderbilt University Hospital on Dec 2, 1930, complaining of diarrhea. The onset was two months prior to admission with blood and pus in the stools, moderate tenesmus and constant but not severe griping pain in the left lower abdominal quadrant. The coexistence of fever could not be established. These symptoms continued, and the patient frequently had eight and nearly always six rather thin stools daily, until admission. Six weeks prior to admission anorexia and insomnia (not subsequent to pain) developed. One week before admission the patient had a severe chill, associated with nausea and vomiting. Following this he believed he had fever. He had had hemorrhoids, never acutely sore but inconstantly associated with fresh blood in his stools, over a period of five years preceding admission. He resided continually in Tennessee except for occasional short visits. His attack began while he was on a trip into Ohio.

On admission, the pulse rate was 100, the temperature, 99.8 F, and the respiratory rate, 22. The skin was loose and flabby, with marked loss of subcutaneous fat. Body lice were present. The palpable lymph nodes were not enlarged or tender. The lungs were clear. The heart was normal. A palpable, roughly defined, movable mass was present in the left lower abdominal quadrant. Numerous hemorrhoids were present. The extremities were normal. Reflexes were normal.

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From the Department of Pathology, Vanderbilt University School of Medicine.

1 Schmieden, V, and Westhues, H. Zur Klinik und Pathologie der Dickdarmpolypen und deren klinischen und pathologisch-anatomischen Beziehungen zum Dickdarmkarzinom, Deutsche Ztschr f Chir **202** 1, 1922.

2 Henke, F, and Lubarsch, O. Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, vol 4, pt 3, p 847.

On the day following admission the patient had twenty-four bowel movements. He was given numerous sedatives to check the diarrhea, but with only moderate success.

The urine was essentially normal. The blood count showed white blood cells, 5,500, red cells, 3,250,000, hemoglobin, 57 per cent, polymorphonuclears, 75 per cent, and polymorphonuclear basophils, 15 per cent. The Wassermann reaction was negative. The blood serum proteid showed total, 5.4 mg, albumin, 3.6 mg, globulin, 1.85 mg, and albumin-globulin ratio, 2. The stools were frankly soft, bloody and purulent. Smears of stool showed a mixed flora and were negative for parasites. Proctoscopic examination showed multiple bleeding polypoid and ulcerated masses of the rectum. Roentgen examination with barium enemas showed marked narrowing of the rectum, with spasticity, constant but variable in degree. The region of the sigmoid showed fine irregularity, with nodular filling defects of the upper portion, suggesting polyps.

The patient remained in the hospital for four months and a half, with no real improvement. On March 8, 1931, exploratory laparotomy was performed. A large mass of perisigmoidal scar tissue was found about the sigmoid rectum. The incision was closed without further operation. Ten days after operation the incision broke open. No marked contamination occurred. The wound was reclosed. During treatment massive edema of the left leg developed, associated with a cylindric left popliteal mass. The patient died seventeen days after the laparotomy.

*Postmortem Examination One Hour After Death*—The body was profoundly emaciated and multiple decubiti were present over the back and buttocks. A recent gaping surgical incision (laparotomy) was present, from which serosanguineous exudate was dripping. Smears from this wound showed gram-positive coccoidal bacteria. The superficial veins over Poupart's ligament on the left were markedly dilated. A definite cylindric mass was palpable in the left popliteal region and in the medial portion of the femoral triangle. The entire left leg was markedly edematous, and pitted on pressure.

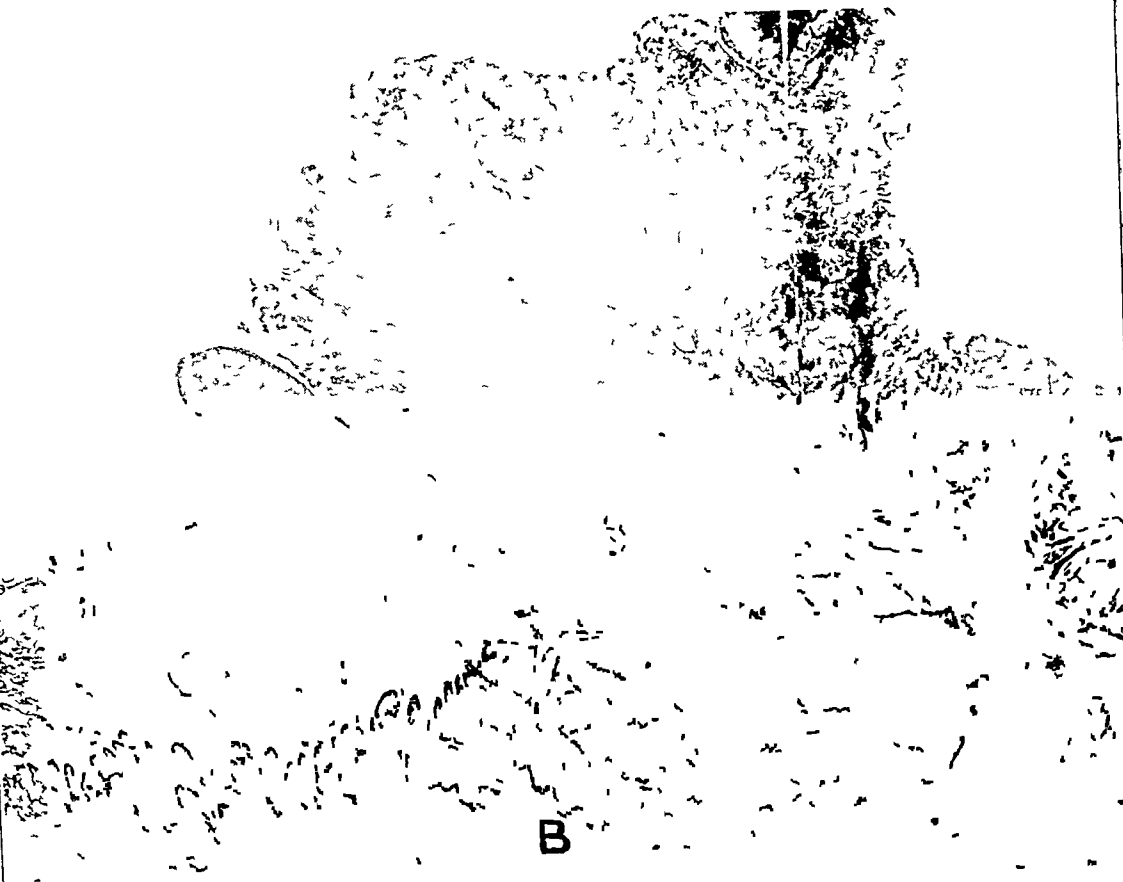
The fatty tissue of the mesocolon, particularly the mesosigmoid, was coarsely trabeculated by dense bands of scar tissue which fixed the entire mesosigmoid and rectum rigidly to the abdominal wall in the region of the mesenteric attachment. The lymph nodes were small throughout the mesocolon and free from grossly recognizable tumor metastases. The heart was remarkable only for occasional scars and moderate brown atrophy. Multiple thrombi in the pulmonary arterial branches were associated with numerous acute infarctions of the lungs. There was thrombosis of the left popliteal, femoral and iliac veins. The liver and spleen were essentially normal, as were the kidneys, pancreas, suprarenals, stomach, duodenum, jejunum and ileum.

Beginning in the cecum and increasing in number and size as the sigmoid was approached were multiple sessile and pedunculated, rounded, gray, friable polyps. Associated with them were areas of ulceration. Some of the polyps were as much as 2 cm long and 1 cm in cross-section. Those of the colon above the sigmoid were for the most part covered by velvety epithelium. Those of the sigmoid and rectum, much the largest, were frequently ulcerated, their tips being necrotic and hemorrhagic. In no instance was there evidence of invasion of the submucous layers by epithelial tissue, although both the mucosa and the submucosa were frequently scarred and rich in granulation tissue beneath large ulcerated polyps. From such regions as these dense cicatricial bands frequently extended far into the extramuscular fatty tissue of the sigmoidal mesocolon and rectum. Sections for microscopic study were taken from all portions of the colon, including both polypoid and nonpolypoid areas.





A



B

Fig 1—*A*, the colon, showing multiple pseudopolyps and ulceration *B*, section under low magnification showing a pseudopolyp with surface ulceration To the left is a submucous nodule of the specific granulation tissue that composes the larger pseudopolyp

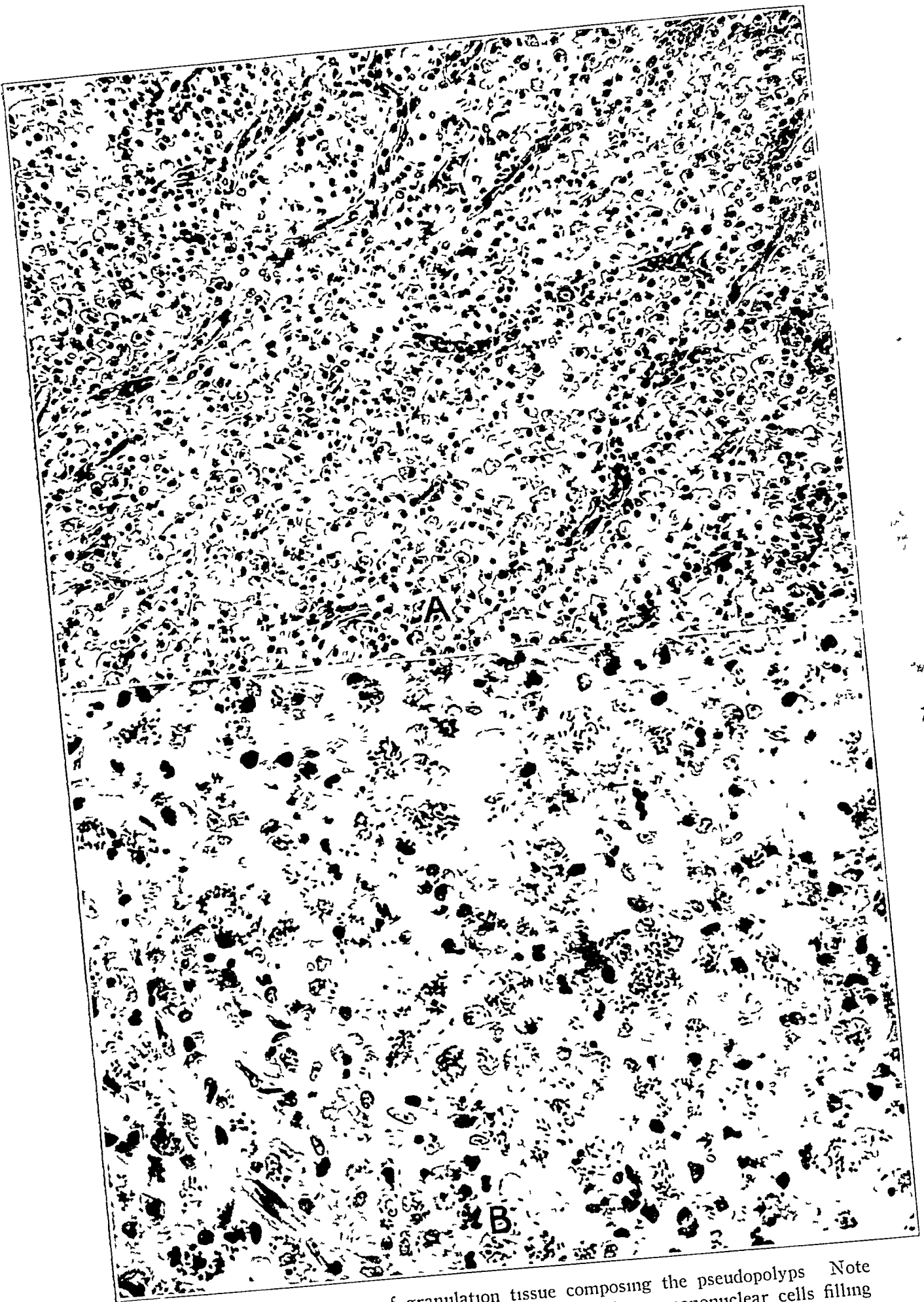


Fig 2—A, the type of granulation tissue composing the pseudopolyps. Note the delicate trabeculae carrying capillaries and the large mononuclear cells filling the interstices. B, distribution of micro-organisms in the inflammatory cells.



Fig 3—*A* and *B*, intracellular bacilli often arranged about spherical spaces (Goodpasture's stain) *C*, spherical intracellular inclusions

On microscopic examination it was seen that the polypoid masses abruptly interrupted the surface contour of the colon. Often the mucosa was simply elevated to form a mound, but more frequently there were definite pedunculated polyps. The adjacent glandular structures, frequently hyperplastic, were prolonged, together with the muscularis mucosae, a short distance outward as a surface layer for the pedicle of the polyps. Beyond this both glands and connective tissue structures were obliterated by a massive aggregation of cells between which coursed only blood vessels and delicate fibrous tissue trabeculae. The surfaces of such polyps were frequently ragged and amorphous. The large mononuclear cells were situated in the submucosa and extended in a compact mass almost to the stratum muscularis, where they were limited by the outermost layers of the submucosal connective tissue. Similarly those masses of cells which simply elevated the mucosa without ulceration were distinctly circumscribed and confined to the submucosa and mucosal stroma, but were unencapsulated.

Cytologic study of the polypoid and circumscribed intramural cell clusters revealed a profound inflammatory reaction characterized primarily by cellular exudate. The inflammatory cells were practically all of the same kind. They were large mononuclear cells with abundant cytoplasm stained a pale pink and faintly granular in hematoxylin and eosin preparations, possessing dense, small nuclei. They bore a resemblance to the Mikulicz cells of rhinoscleroma, especially in that they contained numerous bacilli in their cytoplasm. They were free cells so closely packed throughout lymphatics and tissue spaces as to obliterate almost completely the normal architecture. No mitotic figures were seen. Frequently small focal areas of necrosis occurred in aggregations deep in the polypoid mass, and these areas were infiltrated with polymorphonuclear leukocytes. And, what is even more striking, the mononuclear cells were fairly uniformly stippled by numbers of small, pink-staining (hematoxylin and eosin) bacillary organisms often arranged in clusters within the cells, and frequently associated with large ovoid or circular, intensely pink, included bodies. Similar micro-organisms were found in numbers at the ulcerated surfaces where there was a polymorphonuclear exudate, but it appeared that the free bacteria might be derived in part at least from rupture and disintegration of the mononuclear cells in which they were confined elsewhere. Small lymph nodes adjacent to the involved colon showed moderate numbers of large mononuclears which contained the bacilli in intracytoplasmic groups.

The organisms, so abundant within the inflammatory cells, were rarely observed in an extracellular position, so seldom in fact that they appeared to have grown only inside the mononuclear cells. With the hematoxylin-eosin stain in tissue fixed in Zenker's fluid the bacteria were faintly pink, by Gram's method they did not retain the gentian violet and by the intensification, basic fuchsin staining of Goodpasture they took an intense purple-black stain. By the last method the intracellular bacteria were frequently found arranged about cystic spaces.

The included hyalin-like oval or spheroid bodies were stained red in the hematoxylin and eosin preparations and brownish purple by the carbolanilin-fuchsin stain. In almost all instances, if included structures were present, micro-organisms were also present, but in many cells micro-organisms were present without included structures. The inclusions bore no demonstrable relationship to the distribution of organisms within the cells.

Many gradations occurred in the state of inflammation of the different polyps studied. In some granulation predominated, but the specific inflammatory cells could always be found in relatively large numbers deep in such polyps.

*Bacteriology*—Fresh tissues preserved at autopsy were, unfortunately, not cultured until they had been preserved in the icebox for three weeks because of a delay in the recognition of the nature of the lesion. At this time, after surface searing, deep cultures from polyps were taken and inoculated on Sabouraud's medium. Twenty-four hours later in all tubes characteristic ovoid, sticky, yellow-gray colonies developed in pure culture. This organism was isolated from six different polyps, but was never encapsulated and was constantly a gram-positive bacillus.

*Animal Inoculation*—Subcutaneous injection of tissue into rabbits and guinea-pigs produced acute abscesses from which a gram-positive bacillus could be grown in pure culture on Sabouraud's medium. Inoculation with the organism transplanted from the polyps to Sabouraud's medium and grown in pure culture produced acute abscesses in rabbits, from which the organism could be recovered, but in which no intracellular organisms were demonstrable. Subcutaneous inoculation of monkeys (*Macacus rhesus*) produced transient acute inflammation which subsided spontaneously after three or four days.

#### COMMENT

So little is known of the origin of polyposis of the colon and the underlying factors associated with its existence that it seems advisable to present this case in which a specific micro-organism appears to have been responsible for a polypoid inflammation of the colon. The clinical symptoms simulated those of ordinary polyposis with ulceration, and occurred in association with structures which bore a close gross resemblance to ordinary polyps of the colon.

The extent of infection indicates that the organism described in these lesions was responsible for the colitis, and its widespread distribution suggests a high degree of pathogenicity at least in susceptible subjects. This type of colitis has not, to my knowledge, been previously recognized either cytologically or bacteriologically.

The relationship of the organism to the individual cells is of interest. Their characteristic intracellular position can hardly be explained on the basis of phagocytosis and seems best interpreted by the supposition of an intracellular growth. The arrangement of the bacteria within the cell about the periphery of spherical spaces also indicates that the cellular cytoplasm is a suitable medium for their multiplication.

Unfortunately, nothing can be said of the origin of the inflammatory cells which are so strikingly typical of this inflammatory reaction. They have the appearance, however, of large mononuclear wandering cells. The origin of the inclusion-like structures within the cells is uncertain. Whether they are phagocytosed structures (which seems doubtful) or products of cellular degeneration has not been determined.

The bacteriologic studies in this particular case are valueless so far as actual demonstration of the etiologic agent is concerned. The organism isolated on Sabouraud's medium may well have been merely a con-

taminant, since in inoculation of animals intracellular organisms could not be satisfactorily demonstrated

The case is reported in order to call attention to a hitherto undescribed polypoid colitis, due, it is believed, to a specific gram-negative, apparently unencapsulated bacillus. The characteristic lesion is a specific inflammatory tissue composed almost entirely of large mononuclear cells which contain within them the etiologic agent

#### SUMMARY

1 A case of ulcerative polypoid colitis, with a typical clinical history of an infectious ulcerative colitis and the roentgenologic findings of polyposis, with suspected malignancy, is reported. This type of lesion in the colon has apparently not been described before.

2 The polyps are composed primarily of accumulations and massive clusters of large mononuclear inflammatory cells which contain the infectious agent.

3 The etiologic agent is a gram-negative bacillary organism situated for the most part within large mononuclear leukocytes. The microorganism has not been cultivated, nor were distinctive lesions induced in animals by inoculation with infected tissue.

# TUBERCULOSIS OF THE MYOCARDIUM

REPORT OF SIX CASES, WITH OBSERVATIONS ON INVOLVEMENT OF  
CORONARY ARTERIES

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While tuberculous pericarditis is not uncommon, tuberculous involvement of the myocardium is decidedly rare. Some idea of the incidence of the latter condition can be gained from the reports of Raviart<sup>1</sup> and Norris,<sup>2</sup> the former finding only 49 cases among 7,683 autopsy reports collected from French and German sources, and the latter 5 cases among 7,319 protocols. In all, we have been able to find reports of only a few more than 200 instances of tuberculous myocarditis (Raviart,<sup>1</sup> Norris<sup>2</sup> and others<sup>3</sup>).

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From the Divisions of Cardiology and Pathology of the Philadelphia General Hospital and the Robinette Foundation of the University of Pennsylvania

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3 (a) Adamson, W W. A Case of Tuberculosis of the Myocardium, J Path & Bact **23** 399, 1920 (b) Anders, J M. Tuberculosis of the Myocardium, J A M A **39** 1081 (Nov 1) 1902 (c) Beifeld, A F. Tuberculosis of the Myocardium with Report of a Case, Tr Chicago Path Soc **8** 104, 1909-1912 (d) Benda, C. New Cases of Tuberculosis of the Myocardium with Report of a Case, Tr Chicago Path Soc **8** 104, 1909-1912 (e) Berger, L, and Miller, J C. Solitary Tuberculosis, Virchows Arch f path Anat **273** 250, 1929 (f) Bettom, I. Cases of Tuberculous Myocarditis with Multiple Nodes, Cuore e circolaz **13** 210 and 223 (May) 1929 (g) Binder, H. Tumor-Like Tuberculosis of the Heart, Zentralbl f inn Med **41** 462, 1920 (h) Brockhausen, K. Unusual Case of Tuberculous Myocarditis, Virchows Arch f path Anat **318** 274, 1929 (i) Carson, W J. Disseminated Tuberculosis, Caseous Tuberculosis of Thymus and Myocardium, M J & Rec **119** 281, 1924 (j) Demme. Beitrage zur Tuberculose des Kindesalters und ein Fall von primarer Tuberculose des Herzmuskels Wien med Bl **10** 1545, 1887 (k) Dillon, E S. Tuberculous Pericarditis with Tuberculosis of Myocardium and Endocardium, M Clin North America **10** 253 (July) 1926 (l) Doerner. A Case of Conglomerate Tuberculosis of the Heart, Diss Jena, 1918 (m) Ellis, A. A Heart Showing Chronic Tuberculosis of the Pericardium with Involvement of the Myocardium, Proc Path Soc, Philadelphia **6** 198, 1902 (n) Gallavardin, L, and Gravier, L. Tuberculous Interstitial

In spite of its apparent rarity, we have secured during the past year six examples of tuberculous myocardial involvement from the postmortem material of the Philadelphia General Hospital. A brief history of these cases follows.

#### REPORT OF CASES

**CASE 1—History**—F. E., a colored woman, aged 51, was admitted to the neuropsychiatric wards of the Philadelphia General Hospital on Oct. 7, 1930, because of dizziness and attacks of unconsciousness of from five to twenty minutes' duration, which first appeared five months before admission. The attacks, probably the result of syphilis of the nervous system, which undoubtedly was present, obscured to a large extent the cardiac symptoms. Evidence of slight congestive cardiac failure in the form of breathlessness and edema were, however, revealed by the history. The family history was irrelevant.

**Examination**—Initial examination revealed a somewhat undernourished middle-aged woman who did not appear acutely ill. Nothing abnormal was found in the examination of the head, neck, lungs, abdomen and extremities. The heart was found to be slightly enlarged and its rate rapid, but otherwise not noteworthy. The blood pressure was 124 systolic and 80 diastolic, the radial arteries showed moderate thickening.

The Wassermann tests of the blood and spinal fluid were strongly positive, and a dementia paralytica colloidal gold curve was present. Other laboratory studies revealed nothing of note. Neither roentgen nor electrocardiographic examination was obtained.

**Course**—During the six months' observation the attacks of unconsciousness became more frequent and finally were accompanied by convulsive phenomena. The patient had a continuously elevated temperature (from 99 to 101 F.), her pulse and respiration rates steadily increased until they were 140 and 40, respectively, just before her death. Preceding death, her lungs, previously normal, began to show basal râles, which led to a diagnosis of bronchopneumonia, the final diagnosis being dementia paralytica and bronchopneumonia.

**Necropsy**—The pericardium was thickened and adherent to the heart and adjacent mediastinal structures, and to the left lung. The heart and attached pericardium weighed 300 Gm. Where the pericardial adhesions could be freed, the epicardial surface was seen to be thickened and white or grayish red. Bulging from the anterior wall of the right auricle and from its appendage was a yellowish-white, irregularly smooth, firm mass, measuring 3 cm. in length, 2.25 cm. in

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except over the roof of the right auricle, where it definitely invaded and destroyed the myocardium (fig 2) No definite caseation was found

Including the epicardium, the left ventricle at its midportion measured 22 mm in thickness, the right, 12 mm, the right auricle in its anterosuperior aspect, 8 mm, and the left, 6 mm The myocardium was a normal reddish brown and was moderately firm The valves, the root of the aorta and the orifices of the coronary arteries showed nothing of importance, while the larger coronary branches, although they showed considerable calcareous infiltration, were patulous wherever dissection permitted inspection

The mediastinal lymph nodes showed early and moderate caseous degeneration, while the bronchial nodes were large and calcified The pleura was neither thickened nor adherent, and no free fluid was present The lungs showed nothing of



Fig 2 (case 2) —A, tuberculous pericarditis, and B, secondary invasion of the right auricle

note, except healed apical tuberculosis about the size of a ten-cent piece in the upper right lobe

The lower portion of the second, the greater portion of the third and the intervertebral disk between these lumbar vertebrae showed typical tuberculous necrosis Beneath the iliopsoas muscle of each side was a well localized collection of tuberculous pus The pathologic findings in other viscera are indicated in the pathologic summary

*Histopathology of the Heart*—The sections studied were taken from the anterior and superior wall of the right auricle The outer portion of the thick pericardial layer consisted of caseation, while the inner portion showed an active, proliferative, inflammatory process, with many tubercles, giant cells and diffuse fibrosis, which invaded the epicardial fat and auricular muscle The mild form of involvement of the muscle consisted of distention of the fibers by a gelatinous edema, with sparse infiltration of fibroblasts and occasional endothelial cells In this type of involvement the individual fibers stained fairly well, and the nuclei

were apparently undamaged. In other instances the infiltration was more intense and destructive, large and small nodules of endothelial and round cells were found to extend through the muscle and reach the endocardial surface. Accompanying this nodular infiltration was local destruction of muscle. In the two larger arteries, as well as the smaller vessels, a moderate acellular, intimal proliferation was present, though no definite thrombosis was observed. Tubercle bacilli, while not numerous, were found in specially stained sections of the myocardium.

The complete pathologic diagnosis was summarized as follows: chronic adhesive, tuberculous pericarditis, with secondary tuberculous infiltration of the right auricle, tuberculous arteritis, healed apical tuberculosis of the right lung, caseous tuberculosis of the mediastinal nodes and calcification of the peribronchial lymph nodes, tuberculosis of the second and third lumbar vertebrae, with early abscess of the psoas muscles, coronary sclerosis, moderate myocardial fibrosis, hypertrophy of the left, and dilatation of the right, ventricle, moderate arteriosclerosis of the aorta, acute toxic splenitis, chronic passive congestion of the liver, and nephrosclerosis.

*CASE 3<sup>4</sup>—History*—D. S., a Russian laborer, aged 46, was admitted to the medical wards of the Philadelphia General Hospital on Feb. 23, 1931, because of persistent cough, pain in the right side of the chest and progressive weakness of two months' duration. His family history was unimportant.

*Examination*—The essential findings were confined to the lungs and heart. The former showed definite evidence of fibrocaseous tuberculosis, involving both lungs (confirmed by a roentgenogram), the heart showed marked enlargement in the transverse diameter, the heart sounds were distant and feeble, but no murmurs were audible. There were a rapid, regular rhythm and pulsus paradoxus, with a blood pressure of 100 systolic and 60 diastolic. Fluoroscopic examination revealed considerable enlargement of the cardiac silhouette with little systolic excursion of the ventricles. A diagnosis of pericardial effusion was confirmed by pericardial tap. Further laboratory findings revealed a low white blood count and tubercle bacilli in the sputum and pericardial fluid.

*Course*—The patient was treated by repeated pericardial tapplings with reinjections of air, a total of 20 such procedures being performed. As much as 1,200 cc. of fluid was removed at a time. The amounts of fluid withdrawn became smaller and smaller, and eventually there occurred a plastic obliteration of the sac. The exudate was usually serous, although occasionally turbid. Tubercle bacilli were recovered twice.

The temperature ranged from 99 to 104 F., with daily elevations, the respirations ranged from 20 to 30, and the pulse rate, from 93 to 145 per minute. The electrocardiogram on Feb. 18, 1931, showed extremely low amplitude of the ventricular complexes in all leads, with inversion of the T waves in leads I and II. For two months the patient did well, showing a surprising lack of symptoms. About May 1, 1931, however, numerous auricular extrasystoles were noted and remained in evidence. From this point on the patient grew progressively weaker, and death occurred rather unexpectedly on June 1, 1931.

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<sup>4</sup> Several months before death, Dr. Thomas Klein (*Treatment of Tuberculous Pericarditis with Effusion by Artificial Pneumopericardium*, *Tr. Am. Climat. & Clin. A.* 47:61, 1931) reported this case from the point of view of the benefit of frequent tapping and the production of pneumopericardium in preventing the reaccumulation of fluid. At the time of his report, as will be pointed out, it is probable that the myocardium had not yet become involved.

The clinical diagnosis was fibrocaseous tuberculosis of both lungs and tuberculous pericarditis, with probable tuberculous myocarditis

*Necropsy*—The parietal and visceral layers of the pericardium were uniformly thickened by fibrocaseous tuberculosis. In many places the layers were loosely adherent, and the sac obliterated, while in others loculations contained small amounts of thick, greenish-yellow fluid. The heart proper was apparently slightly decreased in size, although its walls, including the epicardium, were markedly thickened. The left ventricle measured 25 mm in thickness at its midportion, the pericardial caseation contributing 10 mm of this thickness, the right ventricle, 10 mm, half of which was formed by pericardial exudate. Tuberculous involvement of the myocardium was found in a small portion of the right auricle lateral to the orifice of the superior vena cava. The muscle at this site was pale and gelatinous in appearance, and the overlying pericardium could not be dissected away.

The tuberculous involvement of other organs is indicated in the pathologic summary

*Histopathology of the Right Auricle*—The epicardium was greatly thickened by caseation and tuberculous granulation tissue. The latter showed its greatest cellularity at the border of the myocardium, into which there was occasional patchy infiltration of groups of large endothelial cells, the cytoplasm of which was often acidophilic. These focal collections were small, scattered and not accompanied by caseation, and contained an occasional giant cell. The muscle fibers were moderately swollen and in some areas disintegrated. The focal necrotic areas contained large endothelial cells and lymphocytes. There was also observed widespread interstitial edema, which in places had a gelatinous appearance. The endocardium was not involved except at one point, where a focal cellular collection had developed, which extended almost to the endocardial surface, however, no ulceration or thrombosis had developed. Large blood vessels were not seen in these sections, but small vessels, particularly arterioles, showed a remarkable endothelial hyperplasia. Occasional perivascular collections of round cells were also noted.

The complete pathologic diagnosis was tuberculous pericarditis, with secondary infiltration of the right auricular muscle, tuberculous arteriolitis, widespread fibrocaseous tuberculosis of both lungs, complicated by tuberculous bronchopneumoma of the left lower lobe, terminal miliary tuberculous invasion of the spleen, kidneys and liver, and caseous, tuberculous, mediastinal lymphadenitis.

*CASE 4—History*—E. H., a colored woman, aged 26, was admitted to the wards for patients with tuberculosis of the Philadelphia General Hospital, on May 6, 1931, because of a productive cough, progressive loss of weight and a chronic, discharging lesion of the left foot. Her symptoms began in May, 1930, following an attack of pleurisy, and had since been progressive. In July, a slight trauma to the left ankle led to the development of an abscess, which did not heal after incision. The patient's past and family history revealed nothing of note.

*Examination*—The essential findings revealed by examination were evidence of tuberculous infiltration diffusely disseminated throughout both lungs, with cavitation at the apex of the right lung. The heart was moderately enlarged in the transverse diameter, no murmurs were audible. The blood pressure was 95 systolic and 60 diastolic. There was a large chronic ulcer on the dorsum of the foot, from which there was considerable drainage with a foul odor.

*Course*—The temperature ranged from 99 to 103 F and the pulse rate, from 100 to 130. The results of the laboratory studies were not of importance, except that the roentgen examination revealed transverse enlargement of the heart and disappearance of the normal contour of the left border, in addition to acute pul-

monary tuberculosis Progressive asthenia culminated in death, on May 26, 1931 The clinical diagnosis was bilateral, chronic ulcerative tuberculosis, tuberculous osteomyelitis of the left ankle and tuberculous pericarditis with effusion

*Necropsy of the Heart*—The heart and its thickened pericardial sac weighed 600 Gm The parietal and visceral pericardium was the seat of an advanced caseous tuberculosis and was so adherent that these layers could be separated only with difficulty The myocardium was pale and exceedingly soft Except for the overlying thickened adherent pericardial layers, which measured from 1 to 3 cm, the ventricular walls were not enlarged There was no definite myocardial infiltration, except in the roof of the right auricle, where the muscle over a small area had a yellowish-gray, almost gelatinous, appearance At this point its demarcation from the thickened pericardium was obscured No gross caseation was seen, nor were any points of endocardial ulceration present There was no pathologic complication of the veins, and the lumens of the coronary arteries were grossly normal (The important pathologic findings in other organs are indicated in the summary of the pathologic examination)

*Histopathology of the Heart*—Section of the right auricle showed the epicardium to be tremendously thickened by fibrocaseous tuberculosis The thickened pericardium could be roughly divided into an outer layer of caseation and an inner cellular layer with dense infiltration of endothelial and round cells, accompanied by numerous giant cells In some fields the myocardium showed marked focal parenchymatous degeneration, the striations having disappeared and the fibers having disintegrated, a poorly stained seminecrotic mass of fibrils remained, into which a sparse collection of epithelioid cells had infiltrated In other fields there were focal collections of large endothelial cells, many of which had eccentric nuclei and more or less acidophilic cytoplasm In one such focus there was a large giant cell, but caseation was not present The small capillaries showed marked endothelial hyperplasia

A second section through the right ventricular wall also showed a thick, cellular, tuberculous infiltration of the epicardium, most dense immediately outside the myocardium Occasionally small clusters of large endothelial cells were seen within the myocardium, usually around the lymphatics or near small blood vessels

A third section taken through the ventricular septum included the anterior descending artery The latter was adjacent to a large tuberculous lesion in the epicardium, but its adventitia was not infiltrated by it It showed, however, a marked proliferation of the intima, which was almost uniformly involved, the thickening being produced, not by cellular infiltration, but apparently by swelling and vacuolization of the intima The elastic laminae were intact, and the media was normal throughout The changes due to ordinary arteriosclerosis were not present

The complete pathologic diagnosis was tuberculous pericarditis, with secondary infiltration into the right auricle, tuberculous arteritis of the anterior descending coronary artery, generalized caseous, nodular tuberculosis of both lungs, with multiple secondary abscesses, caseous mediastinal glandular tuberculosis, and mild tuberculous infiltration of the spleen

CASE 5—*History*—C J, a colored boy, aged 16, entered the medical wards of the Philadelphia General Hospital on May 11, 1930, because of precordial pain, breathlessness and cough Indefinite pain in the upper right side of the abdomen was first noticed three months before admission and was soon followed by dyspnea The pain soon changed its site to the precordium, and there became permanent and extremely severe Cough was present but not striking, and had never been accompanied by hemoptysis Neither the past nor the family history was important

*Examination*—On initial examination, the patient was found to be toxic, restless and harassed by severe precordial pain. No evidence of significant abnormalities were found in the head, neck, lungs, abdomen and extremities. Two important cardiac findings—great enlargement and muffled sounds—led to a diagnosis of pericardial effusion. After two unsuccessful pericardial taps, the diagnosis was changed to adhesive tuberculous pericarditis.

*Course*—During the first three months of observation, the patient improved slightly. Thereafter his course was gradually but steadily downward. In view of the increase in the size of the cardiac silhouette, a third pericardial paracentesis was performed, on Sept 28, 1930, and yielded 8 cc of thick, greenish, necrotic material, which contained many tubercle bacilli. This proved the clinical diagnosis. Evidences of cardiac failure became more and more marked, pulmonary congestion

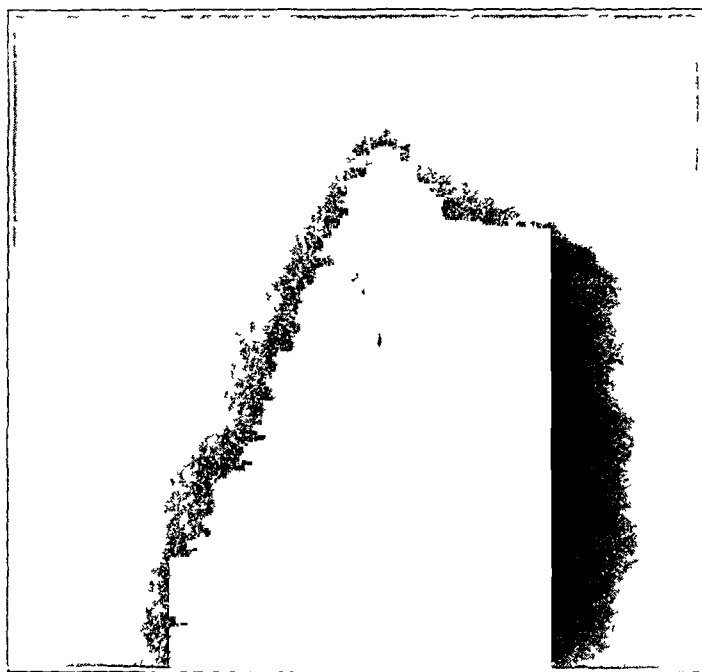


Fig 3 (case 5) —Roentgenogram taken on Nov 15, 1930. The diagnosis was tuberculous pericarditis.

and edema progressively increasing, the pulse rate rising, and auricular fibrillation finally developing shortly before death, on Nov 4, 1930.

During eight months' observation the temperature ranged between 99 and 101 F. Many leukocyte counts ranged between 6,000 and 11,000, with normal differential counts. The Wassermann reaction, the chemical examination of the blood and blood cultures gave negative results, and repeated examinations of the sputum failed to reveal tuberculosis bacilli. All roentgen examinations (fig 3) showed the lungs to be uninvolved by tuberculosis and revealed a large cardiac silhouette that could not be differentiated from pericardial effusion. The electrocardiogram, as early as April 10, 1930, showed definitely inverted T waves in leads I and II, and by Oct 2, 1930, auricular fibrillation and ventricular complexes of extremely low amplitude followed by inverted T waves. The clinical diagnosis was well established as tuberculous pericarditis with caseous necrosis, death resulting mainly from cardiac failure.

*Necropsy*—The heart and adherent pericardium weighed 2,000 Gm (fig 4). When the pericardial sac was opened, a fairly large amount of necrotic caseous material escaped from multiloculated cavities, the spaces of which were lined by grayish-white, shaggy, caseous tissue. The adherent pericardium was involved in a diffuse caseous tumor formation, which extended from the outer surface of the



Fig 4 (case 5) —Massive tuberculous invasion of the entire heart (The heart is viewed from the posterior aspect) Note the pericarditis—the massive, caseous invasion of the right auricle and right ventricle, *CT*—and the narrow zone of remaining ventricular muscle, *m*. Note endocardial tubercles, *T*, and tuberculous ulceration, *TU*.

pericardium into the depth of the underlying heart muscle. This process infiltrated all the chambers of the heart, particularly the ventricles, the thickened caseous wall measuring 35 mm in various portions of the left ventricle and 50 mm in the right ventricle. Demarcation between this process and the remaining cardiac

muscle was followed with difficulty because of the finger-like infiltration of the caseous mass into the myocardium. In some places the caseation reached the endocardium, causing localized swellings and ulcerations. Beyond the zone of active caseation, the adjacent muscle had undergone a grayish, gelatinous degeneration.

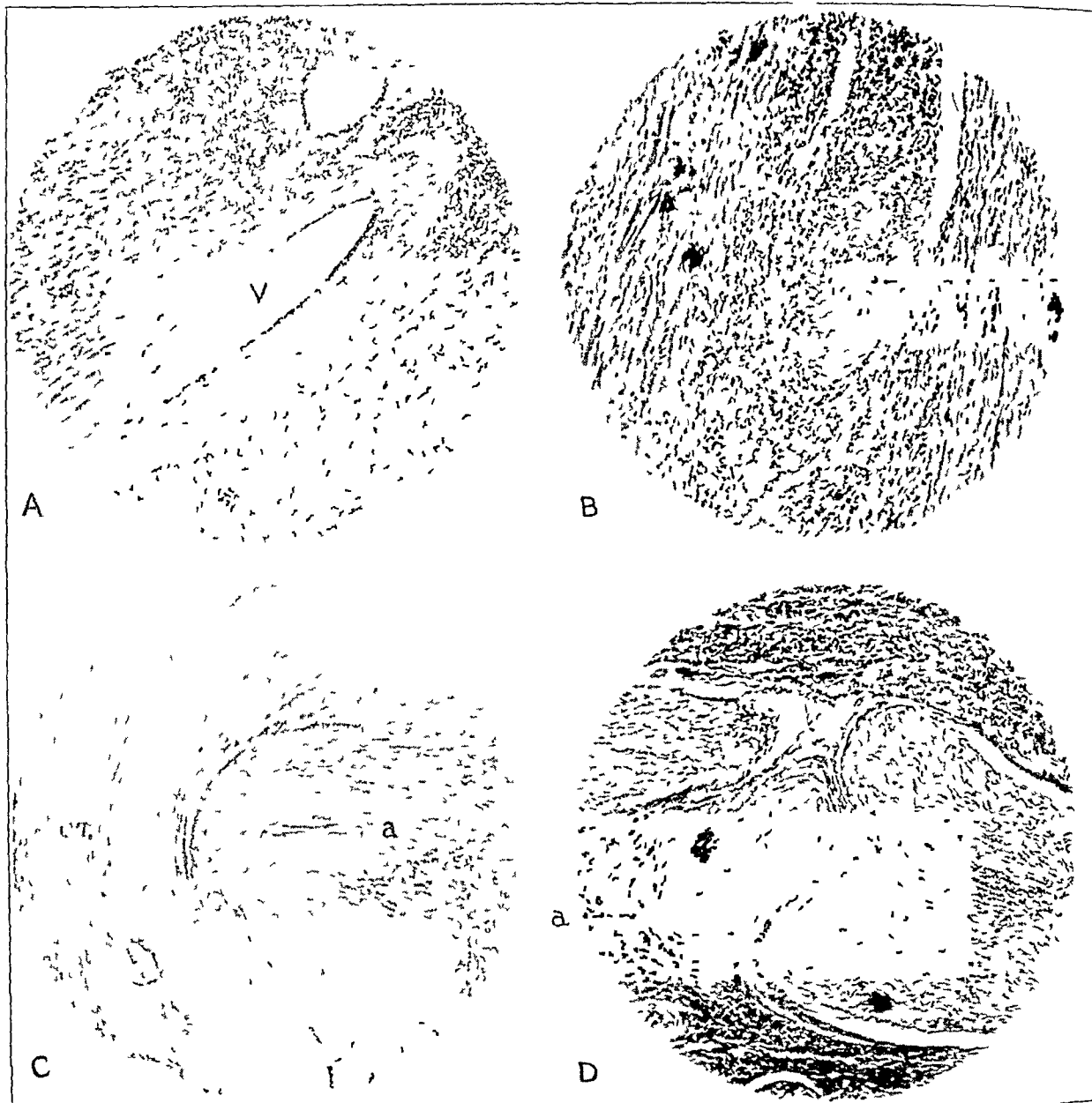


Fig 5 (case 5) —*A*, diffuse tuberculous infiltration of entire wall of coronary vein, *V*, *B*, thrombosis and necrosis of the wall of the coronary vessel, probably a vein, *V*, *C*, diffuse intimal thickening of the coronary artery, leading to almost complete occlusion, *a*. Note the marked perivascular tuberculous infiltration and the massive caseation, which apparently compresses the artery, *CT*, *D*, small branch of coronary artery, *a*, showing diffuse intimal thickening and thrombosis.

to such an extent that in considerable portions of the heart, particularly in the right ventricle, there was no remaining cardiac muscle of normal appearance. The

papillary muscles and valves appeared to have escaped this invasion, although at the auricular-ventricular junction, caseation had extended into the valve rings

The coronary vessels could be followed for only a short distance beyond their point of origin, being involved in and destroyed by the diffuse infiltration. No remnant of the main posterior descending artery or vein could be found, and the remaining portion of the left anterior descending artery could be followed for only a short distance from its point of origin. The portion of this vessel that was recognized showed a very narrow lumen and was flattened and compressed by the extensive surrounding tuberculous process<sup>5</sup>

The mediastinal lymph nodes were markedly enlarged, white, soft and caseous. The pleura and the lungs showed no evidence of tuberculosis. The latter, however, were compressed by the enormous heart, and the right lower lobe contained numerous recent infarcts, probably the result of emboli composed of necrotic tuberculous material from ulcerations in the right auricle, which had occurred terminally. The spleen was large and firm (weight, 240 Gm) and contained an infarction. The liver weighed 1,700 Gm, but showed no change except congestion, while the kidneys were not remarkable.

*Histopathology*.—Sections from the ventricles and auricles showed massive and widespread tuberculous pericarditis and myocarditis. The infiltration occurred as a wide zone of caseous necrosis and granulation tissue, which destroyed the outer portions and in some places the entire thickness of the myocardium. In general, from without inward, a cross-section of the heart showed the following distinct zones: an outer, yellowish-white zone, which was the widest and consisted of caseous necrosis; a middle zone, which was grayish and was made up chiefly of granulation tissue; and a brownish inner zone which consisted of the remaining undestroyed cardiac muscle. In the outer zone, small streaks of dark gray, gelatinous appearance indicated the course of blood vessels. Both the caseous portion and the zone of infiltration contained innumerable tubercle bacilli.

In many portions of the right auricle and in some parts of the left ventricle the myocardium was involved throughout its entire thickness. In some locations, a narrow subendocardial layer of muscle was still preserved, but even this was the seat of an acute interstitial myocarditis. This interstitial infiltration consisted of large and small foci of endothelial cells, lymphocytes, plasmocytes, typical Langhans' cells and occasional polymorphonuclears. Accompanying this infiltration were occasional tubercles. Where the focal collections were relatively large, caseation was present. The rich endothelial proliferation both in and around the small blood vessels in many ways suggested the pathologic involvement observed in rheumatic fever. (This will be discussed later.) The small vessels showed an endothelial hyperplasia, at times of such a degree as to cause almost complete obliteration of their lumens. In the subendocardial zone of undestroyed muscle that we are describing, the myocardium was comparatively well preserved except for areas in which cellular infiltration had progressed to the stage of local caseation. Even when surrounded by infiltrating cells, the individual fibers preserved their striation, stained fairly well and showed normal nuclei.

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<sup>5</sup> The means by which the existing heart muscle was nourished in the presence of almost complete destruction of the coronary arteries and veins is discussed in another paper (Bellet, S., Gouley, B. A., and McMillan, T. M. Nourishment of the Myocardium Through Thebesian Vessels in a Heart in Which the Large Coronary Arteries and Veins Were Destroyed by Tuberculous Myocarditis, *Arch. Int. Med.* 51: 112 (Jan.) 1933).



As already indicated, the coronary vessels were involved to an extreme degree, even the largest arteries being entirely destroyed (As the other five cases also were subject to the same process to a lesser degree, tuberculous involvement of the coronary arteries will be considered as a whole elsewhere)

The complete pathologic diagnosis was tuberculous adhesive pericarditis, tuberculous myocarditis, tuberculous arteritis and arteriolitis, and destruction of coronary arteries and veins, tuberculous mediastinal lymphadenitis, and terminal miliary tuberculosis of the lungs and spleen

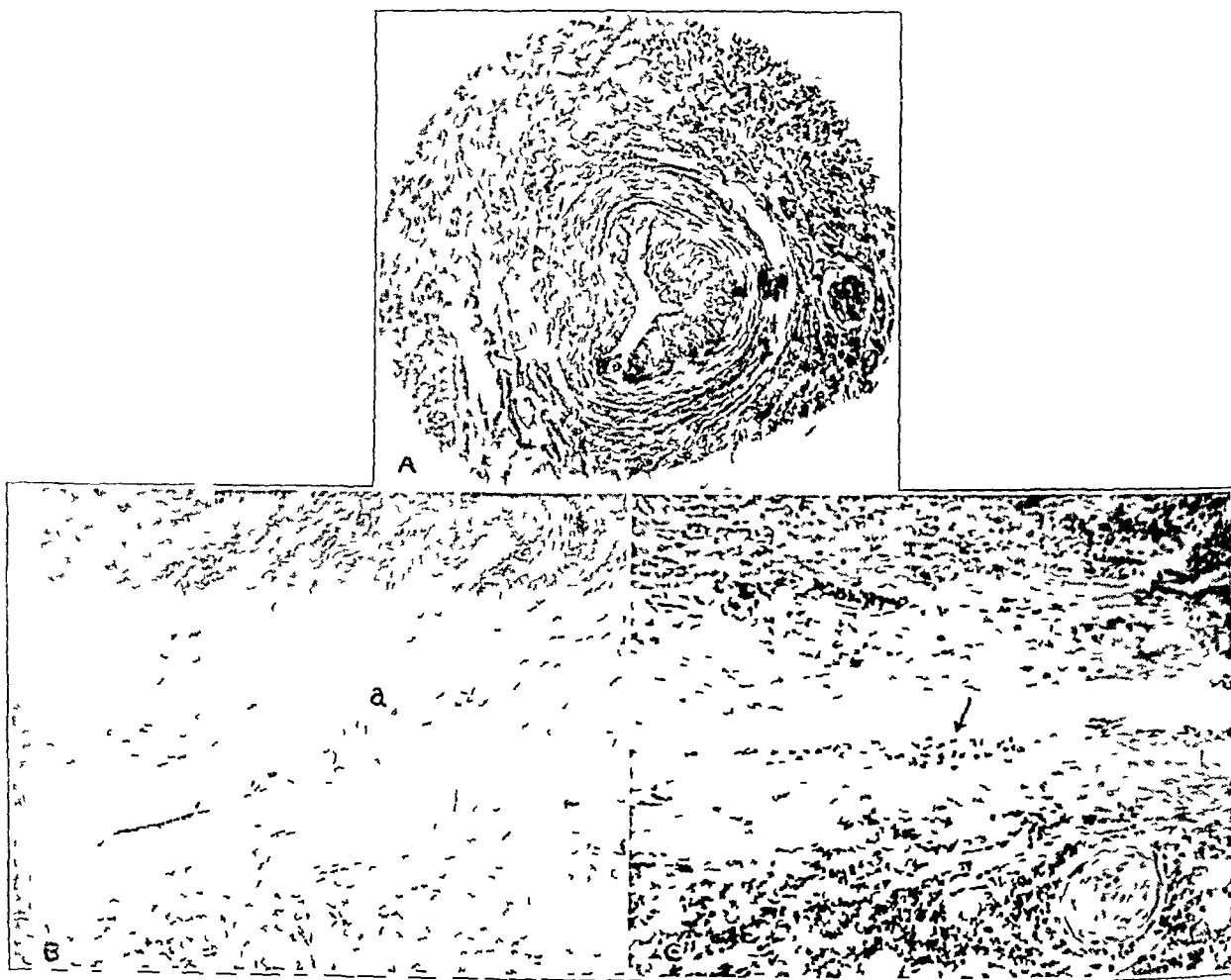


Fig 6 (case 5) —A, branch of the coronary artery, showing typical "contact" tuberculous arteritis. Note the vacuolated noncellular thickening of the intima, leading to almost complete occlusion. B, posterior descending branch of the right coronary artery, a. Note the intimal thickening, in which there is mild cellular infiltration, most of this intimal proliferation appears, however, to be of the "contact" type. The media is not involved. C, intimal tubercle (marked with arrow) beneath endothelium of large vein.

CASE 6—*History*—R S, a colored girl, aged 16, was admitted to the wards for patients with tuberculosis of the Philadelphia General Hospital on Feb 21, 1930, complaining of cough and pain in the lower left side of the chest, loss of weight and weakness. The patient was apparently in good health until January, 1930, when a heavy cold developed, which led to a persistent cough, progressive weakness

and a loss in weight of 25 pounds (11.3 Kg). No history of hemorrhages or night sweats was obtained. The family and past histories revealed nothing of note.

*Examination*—The patient was found to be considerably emaciated and extremely ill. Expansion over the right side of the chest was definitely limited, and evidences of consolidation of both lungs and cavitation of the right upper lobe were found. The only findings noted in the examination of the heart were slight enlargement and a systolic murmur at the apex. The abdomen and the extremities were normal.

*Course*—From admission to death the patient had a continuous fever, ranging between 102 and 103 F. The pulse and respiration rates were 110 and 30 respectively. She gradually and progressively grew worse, until death occurred, on May 8, 1930. The clinical diagnosis was chronic ulcerative pulmonary tuberculosis.

*Necropsy*—The heart was approximately of normal size, its weight being 180 Gm. There were a few small, discrete, tuberculous nodules and plaques over

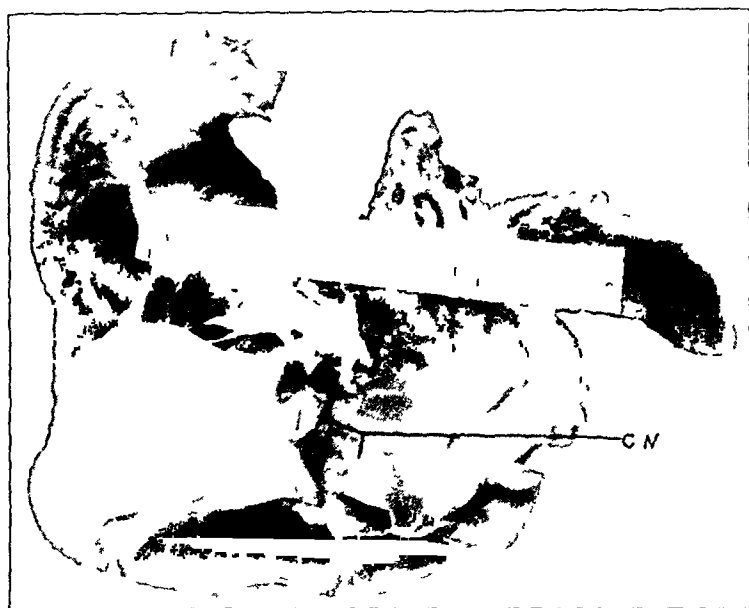


Fig. 7 (case 6)—Isolated caseous nodule, C N, in the wall of the pulmonary conus. There is no direct extension from the epicardium.

the right auricular appendage and the upper aspect of the left ventricle, and at the pericardial attachment to the great vessels. The epicardial lesions seemed definitely to follow the course of the blood vessels. They were small, and in no place were they observed to penetrate into the myocardium. There was, however, a firm, white, homogenous nodule, 1 cm. in diameter, situated in the right ventricular wall, just ventral to the pulmonary artery (fig. 7). This nodule projected into the lumen of the pulmonary conus but did not ulcerate. On its outer aspect a narrow zone of myocardium separated it from the epicardium. The myocardium throughout the rest of the heart showed only a mild pallor. The endocardium and valves showed nothing abnormal. The aorta and coronary vessels were normal.

The mediastinal lymph nodes were moderately enlarged, and were homogeneous and white on section. The central portion of some of these nodules was caseous. Both lungs showed a diffuse nodular tuberculosis with caseation, the left lung showing in addition tuberculous pneumonia involving the entire upper lobe. (The tuberculous involvement of other organs is indicated in the pathologic summary.)

*Histopathology of the Heart*—In certain portions of the pericardium there were diffuse infiltrations of round cells, accompanied by small miliary tubercles. The latter appeared to be quite recent and showed a tendency to follow the course of the blood vessels. As far as we could ascertain, there was no connection or continuity between these epicardial infiltrations and the single nodule noted in the myocardium.

The nodule was definitely caseous, and surrounding it was a dense zone of epithelioid and round cells. It bulged considerably into the lumen of the right ventricle but was separated from the latter by a few stretched myocardial fibers, which had undergone pressure atrophy. A well preserved zone of myocardium was also present between the nodule and the epicardium. Except for that portion in the immediate vicinity of the caseous nodule, the muscle appeared to have preserved its integrity fairly well. An intensive infiltration of cells, chiefly endothelial and round cells, with scarcely any polymorphonuclears, was seen, but only in areas immediately adjacent to the solitary tuberculous nodule. In these same sites, edema, which in places presented an almost gelatinous appearance, was present between muscle fibers.

The large blood vessels showed no abnormalities. Intimal hyperplasia and tuberculous arteritis were not seen. Some of the small vessels, chiefly arterioles, showed a slight thickening of the intima. This was observed not only near the nodule but in fields somewhat distant from the tuberculous involvement.

The complete pathologic diagnosis was tuberculous pericarditis and tuberculous myocarditis, diffuse nodular tuberculosis of the right lung and tuberculous pneumonia of the left lung, with ulceration of the lower lobe, tuberculosis of the mediastinal, retroperitoneal and mesenteric nodes, and tuberculous perihepatitis, serositis and enteritis.

#### COMMENT

*Age*—In a series of 73 cases of myocardial tuberculosis collected from the literature by Anders,<sup>3b</sup> 40 per cent of the patients were less than 16, and 40 per cent were between 16 and 45. Only 5 of the 73 patients were above 60. Raviart<sup>1</sup> was able to collect from the literature 185 reported cases of myocardial tuberculosis, of which 182 were regarded by him as authentic. In 124 of these cases, only 23, or 18.5 per cent, were 40 years of age or older, 8 were between 60 and 70, and 4 between 70 and 80 years.

*Site of Involvement*—Anders<sup>3b</sup> regarded the auricles as the chief site of tuberculous myocardial involvement, with the right auricle more commonly affected than the left. Raviart<sup>1</sup> regarded the left ventricle as the main site of involvement, but believed that the right auricle was the chief location of large tubercles.

*Pathologic Classification*—Raviart<sup>1</sup> placed the cases he collected in groups showing the following conditions: (1) gross tubercles or nodules, (2) tuberculous infiltration or diffuse tuberculosis, (3) miliary granulation of the myocardium and (4) tuberculous myocarditis (interstitial, nonfollicular and parenchymatous myocarditis, without any other definite tuberculous cardiac involvement). Adopting and somewhat modifying this classification, we have placed the forms of tuberculous invasion of the cardiac muscle as we have observed it in our cases in

the following groups (1) large tubercle, or caseous tumor (case 1), (2) tuberculous granulation infiltration (cases 2, 3 and 4), (3) widespread massive caseous tumor and granulation infiltration, a combination of types 1 and 2 (case 5) and (4) isolated small tubercle occurring in the course of systemic miliary tuberculosis (case 6)

While all of our cases showed some degree of diffuse cellular interstitial myocarditis, in none of them was this the sole tuberculous lesion of the myocardium, it was clearly secondary

*The Manner in Which Tuberculosis Reaches the Myocardium*—A much simpler and, from the clinical point of view, perhaps as useful a classification of myocardial tuberculosis can be based on the location of the primary lesion and the manner of its spread to the heart. Such a classification would include only these divisions (1) tuberculosis of the myocardium, resulting from direct extension from mediastinal glands—first to the pericardium and thence to the myocardium<sup>6</sup>—and (2) myocardial tuberculosis, resulting from dissemination by the blood stream of tuberculosis from some extracardiac focus

According to such a simple classification, the first 5 cases of our series would fall under class 1. Our cases 1, 2, 3 and 4 represent the type and degree of involvement usually seen. Despite extensive glandular and pericardial lesions, the myocardial involvement consists only in the development of a large tubercle or group of several tubercles appearing as caseous tumors of moderate size with or without accompanying granulation tissue being limited, in the 4 cases under discussion, to the right auricle.

The involvement shown in case 5, although differing from that seen in cases 1, 2, 3 and 4 only in degree and not in type, represents an extreme of infiltration that is rarely seen. Anders,<sup>3b</sup> in 1902, was able to find reports of only 2 cases of so extensive an involvement, and Ravaut,<sup>1</sup> in his large series, only 12. The case recently reported by Thomson<sup>3a</sup> was similar to our case 5, but did not present such extensive destruction.

When tuberculosis reaches the heart by direct extension, the mediastinal lymph nodes and not the lungs are considered to be the focus

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6 It is believed that tuberculosis of the pericardium and the myocardium can be caused by direct contact with an adjacent lymphadenitis, Kast (Ueber eitrige Pericarditis bei Tuberculose der Mediastinal Druse, Virchows Arch f path Anat 96 489, 1884) reported a case in which a caseous lymph node ulcerated into the pericardial sac. The normal lymphatic flow from the heart and pericardium is toward the mediastinal glands, and it is probable that when a pathologic condition in those glands results in lymphatic block, a reversal of the normal current takes place. Thus, with caseous tumor infiltrating the mediastinal and tracheobronchial lymph nodes, there is probably a reversal and eventual stagnation of the lymph flow, followed by establishment of tuberculous foci within the myocardium.

In our 6 cases, mediastinal involvement was present in all instances. In case 5, no evidence of pulmonary involvement, except terminal, was found, while in case 2, the only pulmonary lesion was a healed lesion the size of a ten cent piece. In case 3, there was no old pathologic condition of the lungs, the acute terminal miliary involvement being secondary to the myocardial tuberculosis. The remaining 3 cases did show widespread pulmonary tuberculosis.

We have placed our case 6 tentatively under the second heading of a classification based on the site of the original tuberculous focus and its mode of dissemination. We cannot positively consider that the isolated myocardial tubercle in case 6 had its origin in a blood-borne infection, because of the existence of tuberculous mediastinal glands and even more because of the few small epicardial tuberculous plaques. The type of tuberculosis in the lungs, spleen and other viscera, however, and the fact that the deep-seated isolated myocardial tubercle was separated from the epicardium by a zone of apparently healthy muscle, led us to feel that this lesion was in all probability blood-borne. The great resistance of the heart muscle to tuberculosis is illustrated by the rarity of myocardial involvement during miliary tuberculosis. In the case reported by Blockhausen<sup>31</sup> the tuberculous infection did apparently reach the myocardium by the blood stream.

It should be borne in mind that myocardial tuberculosis may be the means of disseminating the disease and setting up a generalized miliary invasion. We believe this to have been the course of events in case 1. In this instance there was primary glandular tuberculosis, with secondary myocardial involvement, and a final generalized miliary invasion, the tubercle bacilli having escaped from the caseous tumor into the cavity of the right auricle through grossly visible ulcerations.

*Primary Tuberculous Myocarditis*—In a few instances<sup>32, 33</sup> the myocardium has been reported to have been the sole site of tuberculous infection. The evidence presented is not conclusive.

*Diagnosis*—Tuberculous myocarditis is probably more common than is generally believed. It not improbably is present in the form of slight infiltrating lesions in many cases of long-standing tuberculous pericarditis. It has been said that tuberculous myocarditis is a pathologic, rather than a clinical, entity, and that its diagnosis is rarely made in life. Tuberculous involvement of the myocardium probably does not result in the development of many symptoms or signs not present in pericardial involvement alone. The only diagnostic point we observed that we believe is suggestive of a myocardial tuberculous involvement is the development of ectopic rhythms in patients known to have tuberculous pericarditis. In case 5 (a boy, aged 16) auricular fibrillation was present continually for at least three months before death. In

case 2, a clinical diagnosis of this arrhythmia was made. In case 3 many auricular extrasystoles rather suddenly developed, after this the clinical course was downward. It seems probable to us that this disturbance of rhythm may have been the result of the extension of the pericardial process into the right auricular muscle. The observations of Fishberg,<sup>7</sup> in which the auricular fibrillation and flutter were frequently found to result from tumor metastases to the right auricle, are interesting in this connection.

*The Similarity and Differentiation of the Interstitial Myocardial Involvement of Tuberculosis and Rheumatic Fever*—This similarity has been commented on before (Raviant<sup>1</sup> and Brockhausen<sup>3b</sup>). The resemblance results from the fact that in both of these myocardial lesions there is a perivascular cellular infiltration and an endothelial hyperplasia in small blood vessels leading to their occlusion. There are, however, certain features that enable one to differentiate these involvements. Tuberculous invasion is far more cellular and profuse, and is often accompanied by an edema that has a gelatinous appearance. In cases in which there is nodular formation the tuberculous lesion is often much larger than similar lesions seen in rheumatic myocarditis. Moreover, the variety of cells that constitute the Aschoff nodule is seldom seen in tuberculosis. Another important differentiating point is the fact that in tuberculosis the parenchymatous elements, in spite of marked interstitial changes, appear to suffer comparatively little, before the advent of caseation, the myocardial fibers are well preserved. In rheumatic myocarditis, in the active stages of the disease, there is usually seen marked parenchymatous degeneration of the muscle, although the interstitial infiltration may be comparatively sparse. Still another point of differentiation is the fact that involvement of the large coronary arteries to the extent seen in case 5 is rarely seen in rheumatic fever, and when present is of an entirely different type. In the latter disease arterial change is characterized by submiliary focal infiltrations of the adventitia and media, with small, patchy areas of destruction of the elastic tissue, the intima of the large coronary artery is scarcely ever involved to the point of imminent or complete occlusion.

*Tuberculous Involvement of Coronary Vessels*—While tuberculous involvement of arteries is well known and has been frequently described in many organs, it has been observed but rarely in the heart, the only reported instances, as far as we are aware, being those of Brockhausen,<sup>3b</sup> Thomson<sup>3t</sup> and Pic and Morénos<sup>3s</sup>. In their cases, involvement was confined to smaller arteries. In 5 of our cases (cases 1, 2, 3, 4 and 6) only small vessels were affected. In case 5, however, the

<sup>7</sup> Fishberg, A. M. Auricular Fibrillation and Flutter in Metastatic Growth of Right Auricle, *Am J M Sc* **180** 629, 1930.

tuberculous involvement included the very largest divisions of the coronary arteries and in this respect as well as in the type of involvement observed is unusual

Three types of involvement of the coronary vessels were seen (1) formation of intimal tubercles, (2) tuberculous invasion of the adventitia with focal or diffuse involvement of the entire wall, and (3) noncellular thickening of the intima, which, if sufficiently extensive, may lead to vascular occlusion. In cases 1, 2, 3, 4 and 6, only the latter form was seen, in case 5, all of these types of arterial involvement were observed. Only in case 5 were veins as well as arteries affected.

In case 5 many vessels showed small collections of lymphocytes and endothelial cells in the intima (intimal tubercle), as can be seen in figure 6, such intimal invasion in places involved the entire circumference of the vessel (the circular intimal tubercle of Askanazy<sup>8</sup>). The media and adventitia of a vessel showing intimal tubercle formation often appeared to be normal, and we must conclude that the intimal tubercles in such instances had their origin in a blood-borne infection (through the coronary circulation).

Tuberculous invasion of the adventitia with focal or diffuse involvement of the entire wall was seen in both medium and small sized arteries and veins in case 5 (figs 5 *A* and *B*). This type of invasion always occurred in the midst of surrounding tuberculosis, being the result, therefore, of a direct extension from an adjacent perivascular tuberculous lesion.

In case 5 almost all the arterial branches even in the absence of definite cellular invasion, showed thickening of the intima. This consisted of swelling of the subendothelial tissue, unaccompanied by cellular infiltration, it apparently was not the result of cellular hyperplasia. The process had the appearance of an edematous thickening with vacuolization of fibrous tissue. This type of involvement was seen best in the large arteries, though arterial branches of various sizes were affected (fig 6 *A*). Occasionally, in the larger vessels, the media was likewise swollen, the muscle cells vacuolated and the distinction between media and intima lost, for both had a spongy appearance. The intimal thickening either involved the entire circumference of the vessel or was localized and projected into the lumen as a rounded knob. The lining endothelium was intact. The lumens of involved vessels were narrowed and in some instances completely closed by an approximation of the intimal surfaces or by the formation of a thrombus. This type

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<sup>8</sup> Askanazy, quoted by Jores, L., in Henke, H., and Lubarsch, O. *Handbuch der speziellen pathologischen Anatomie und Histologie*, II Herz und Gefasse, Berlin, Julius Springer, 1924.

of involvement has long been recognized in the lung and may be called "contact endarteritis"<sup>9</sup> The condition has a characteristically spongy and vacuolated appearance It is distinct from the intimal tubercle in that it is noncellular and is apparently not dependent on the presence of tubercle bacilli in the intima (fig 6A) (We have occasionally seen it in syphilis, and it may possibly occur in other infections) In many locations the lumens of already thickened blood vessels were further narrowed by compression of surrounding caseous masses (fig 5C) The proximal portions of the large coronary arteries, although surrounded by caseation, were enclosed within jackets or islands of cellular infiltration having a gelatinous aspect Before some of the large vessels became completely destroyed, lumens were rendered slitlike by compression and intimal thickening

#### SUMMARY

1 Six cases of tuberculosis of the myocardium are reported, the ages of the patients being 16, 16, 26, 46, 51 and 72 years Four were male, and 2 were female, 4 were Negroes, and 2 were white people

2 These cases represent the different types of tuberculous myocarditis that have hitherto been reported A simple classification is suggested, based on the mode of dissemination and the type of lesion (a) myocardial tuberculosis, secondary to mediastinal glandular and pericardial tuberculosis, and (b) as part of systemic miliary tuberculosis

3 Involvement of the coronary arteries, in one case to an unusual degree and in the other cases to a slight degree, is reported, and the various types of tuberculous arteritis are described (a) diffuse tuberculous arteritis, involving all the vessel coats, (b) intimal tubercle without involvement of other vessel coats, as a result of blood-borne infection, and (c) a type of arterial involvement by tuberculosis (contact arteritis) previously not described in the heart, affecting not only the small, but also the large, coronary arteries and leading to narrowing of their lumens and even to complete occlusion

4 The occasional similarity of rheumatic and tuberculous myocarditis is noted, and a differential diagnosis is outlined

5 The probability of ectopic rhythm, resulting from the tuberculous infiltration of the right auricle, is discussed

The following chiefs of service, Drs C A Aitken, Robert G Torrey, Edward A Strecker, Joseph McIver and John McLean, and the following pathologists, Drs Morgan, Robson, Bortz, Yinger and Custer, permitted us to report these cases

9 This type of intimal hyperplasia has been observed in the smaller arteries in the vicinity of tuberculous infiltration in other organs, notably the lungs and meninges It may be called "contact endarteritis" (Opie, E Personal communication)



# PARADOXICAL BREATHING

EPHRAIM KOROL, M D

LINCOLN, NEB

Paradoxical breathing means the deflation of a lung or of a portion of a lung during the phase of inspiration and the inflation of the lung during the phase of expiration

Paradoxical breathing occurs in all air-breathing vertebrates. It depends on the same anatomic factors as the residual air and seems to serve the same purpose

## DATA FROM COMPARATIVE PHYSIOLOGY

During the evolution of the air-breathing apparatus, provisions were necessary for the dilution of the oxygen of the air,<sup>1</sup> and for its saturation with moisture. In the water, where the amphibian ancestors of modern man lived, the concentration of oxygen is less than 1 per cent, in the atmosphere the concentration is nearly 20 per cent. Among the morphologic adaptations to air breathing, the following are of interest

1 The respiratory passages become long and narrow, a constriction develops in the air tube (the glottis), which narrows in expiration. This arrangement leads to the accumulation of residual air in the lungs.

2 Respiratory movements occur with the glottis and nares closed, directly bringing about an interchange of air between the several portions of the respiratory tract. In the adult amphibians the normal respiratory cycle consists of (a) Aspiration. Air is sucked in from the atmosphere into the mouth and pharynx, with the nares open and the glottis closed. (b) Expiration. The glottis opens, and the nares close, stale air escapes from the lungs into the mouth and mixes with the fresh air therein. (c) Inspiration. The muscles of the mouth and pharynx contract and press the air mixture into the lungs. Frogs thus always breathe impure air, and their lungs are protected from the dry atmospheric air rich in oxygen. In reptiles the respiratory cycle consists of (a) inspiration, (b) expiration with the glottis open, and (c)

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1 Keith, Arthur. Respiration in Frogs, *Nature* **69** 511, 1904. Jordan, M. J. *Allgemeine vergleichende Physiologie der Tiere*, Berlin, W. de Gruyter & Co., 1929, p. 132

expiration with the glottis closed. During the last mentioned phase an exchange of air occurs between the membranous air sac and the lung proper. This third stage of reptilian respiration is of life-saving importance in snakes, in which the trachea may be compressed for hours during the prolonged act of swallowing large objects.

In birds, an interchange of air between the lungs and air sacs also occurs physiologically (and is of vital importance during the act of flying when the chest must be kept rigid) <sup>2</sup>

In the human new-born baby the first expiration (the first cry) is accompanied by a contraction of the glottis. The air drawn into the lung with the first inspiration is but partly expelled into the atmosphere, a portion of the inspired air is entrapped in the infundibula (residual air), another portion is pressed, via the bronchial intercommunications, into the apical and mediastinal portions of the lungs (paradoxical breathing).

In birds and reptiles the air sacs are supplied by the systemic circulation, the contained air is not vitiated as the systemic blood is not oxygenated. In mammals, the air sacs have been incorporated into the lungs proper, all portions of the lungs are traversed by the pulmonary blood vessels. Residual air and paradoxical breathing in mammals mean breathing of stale air. The mammals have become well adapted to atmospheric air, but the anatomic structures leading to residual air and rebreathing have persisted and are of doubtful utility. In labored breathing, the result of effort, and in dyspnea resulting from disease of the heart or lungs, the residual air and paradoxical breathing increase the undesirable symptoms. Under certain conditions the symptoms caused by paradoxical breathing may dominate the clinical picture and may be the immediate cause of death (in open pneumothorax, for example).

*Absence of True Muscles of Respiration*—In this connection it must be pointed out that in human beings no specialized muscles of respiration have developed in the sense that the heart muscle is specialized for the circulation of the blood. In fishes and young amphibians the muscles of the mouth carry on the ventilation. The water is taken in through the mouth and is poured out through the gill clefts by a contraction of the pharyngeal pump mechanism. In reptiles, birds and mammals the muscles of the chest and abdomen find increasing use in respiration, as the muscles of the head and neck gradually lose their importance. In turtles, in which the chest and abdomen are rigid, the muscles of the shoulder and pelvic girdles carry on the respiration. In mammals the diaphragm has become a muscular structure, owing to the migration of the lung into the chest cavity the diaphragm comes to lie between the

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<sup>2</sup> Babak, E., in Winterstein. *Handbuch der vergleichenden Physiologie*, Jena, Gustav Fischer, 1911, vol. 1, pt. 2, p. 911.

chest and abdomen in such a way that its contraction enlarges the chest. In mammals the diaphragm thus becomes an important muscle of respiration, owing to its favorable location. In the lower vertebrates the diaphragm has a circulatory function only.<sup>3</sup> It is thus evident that all the muscles of the face, neck, chest, abdomen, spine and extremities may be employed as muscles of respiration. During tranquil breathing, the nerves to the intercostal muscles alone are stimulated, for more active breathing the nuclei of the nerves to the diaphragm and to the scalene muscles are also irritated, in cases of dyspnea all the muscles of the body may be called into use for the ventilation of the lungs.

*Antagonism Between Functions of Locomotion and Respiration*—About the time that lungs were being developed in vertebrates for air breathing and the body musculature was being adapted for ventilation of the lungs, extremities began to develop for locomotion on land. The muscles of the trunk were now requisitioned for uses other than ventilation of the lungs. The chest had to become more rigid in order to protect the viscera from the weight of the animal, which increased as the buoyancy of the water was lost, more rigidity was also necessary to give the muscles of the extremities power to contract. With the specialization of the upper extremities for flight, climbing, manual labor and other functions, the respiratory capacity of the chest was further encroached on. Not only do there occur permanent ossification and consolidation of the portions of the sternum and ribs, but for increased efficiency of the muscles attached to the chest, the efforts of straining, lifting of weights, etc., are made with respiration entirely suspended (generally after inspiration and closure of the glottis). The muscles of the shoulder and pelvic girdles, taking origin from those of the chest, may now contract, the chest remaining rigid and being kept from collapsing by the air entrapped in the lungs. During this activation of the muscles of the chest with the glottis closed, an interchange of air occurs between the different portions of the lungs.

#### PARADOXICAL BREATHING IN HUMAN BEINGS

*Physiologic Considerations*—The interchange of air between the different portions of the lungs is rendered possible by the following circumstances:

- 1 The interbronchial communication between the two lungs is short as compared with the distance between either main bronchus and the source of fresh air at the mouth or nares. The interbronchial space remains patent under all physiologic conditions, while the communication with the atmosphere is frequently abolished by the narrowing or closing

<sup>3</sup> Keith, Arthur. The Nature of the Mammalian Diaphragm, *J Anat & Physiol* **39** 261, 1904-1905.

of the glottis. The obstruction to the atmospheric air may, moreover, be produced at the lips and nares, as in breathing through a mask, whistling, glass blowing or playing of wind instruments.

2 In inspiration, the trachea and bronchi elongate and their lumen increases, in expiration, the respiratory passages shorten and become narrow, the narrowing affecting particularly the glottis. This coordination of the voluntary muscles of the chest and the involuntary bronchial muscle has been ascribed to the action of a respiratory center. However, as Howell<sup>4</sup> pointed out, there is an inspiratory center only. Expiration depends largely on the force of gravity and on the elastic recoil of the lungs. In forced expiration of dyspnea there may occur a spasmodic contraction of the bronchi and glottis partly defeating the purpose of expiration. The antagonistic action of the expiratory abdominal muscles and of the bronchial muscles has long been known from clinical observations. Recently this condition has been demonstrated by means of electrobronchograms.<sup>5</sup> In forced expiratory movements, owing to obstruction at the glottis, air is driven from the more active to the less active portions of the chest.

3 The chest is not uniformly supplied with musculature, and the different regions of the chest differ in their respiratory capacity. Thus the apical region is relatively deficient in muscle, and there is no muscle tissue available to actuate the mediastinal portions of the lungs. Roth<sup>6</sup> and also Metzger and Auer<sup>7</sup> have shown that the intrapleural pressure varies in the different portions of the chest, and that its respiratory fluctuations are greater in the basal portions. In the less active regions of the thorax the pressure relations are nearly those of the atmosphere in both phases of respiration, while in the more active portions the pressure falls in inspiration and rises in expiration. During deep inspiration, air is sucked into the active portions of the lungs not only from the trachea but from the inactive portions of the lungs, during forced expiration, air is expelled not only into the atmosphere but into the inactive portions of the lungs. This inflation of the lungs during expiration is favored by the narrowing of the glottis and trachea accompanying forced expiratory and straining efforts.

4 The ribs are attached to the spine at such an angle that enlargement of the chest, or inspiration, is possible only by elevation of the

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4 Howell, W. H. Textbook of Physiology, ed. 11, Philadelphia, W. B. Saunders Company, 1930, p. 713.

5 Luisada, Aldo. La contractilité active du pulmon, étudiée au moyen de l'électro-bronchographie, Arch. méd.-chir. de l'app. respir. **5** 320, 1930.

6 Roth. Regarding Intrapleural Pressure, Beitr. z. Klin. d. Tuberk. **4** 437, 1905.

7 Metzger, S. J., and Auer, John. The Respiratory Changes of Pressure at the Various Levels of the Posterior Mediastinum, J. Exper. Med. **12** 34, 1910.

ribs Any movement of the body or any posture which results in an elevation of the ribs produces an enlargement of the chest Stretching of the arms and extension of the spine mean inflation of the lungs, provided the glottis is open If these movements are performed with the glottis closed, there will occur an interchange of air between the several portions of the lungs In the erect posture the ribs are inclined downward, the chest is in relative expiration, and there is less residual air in the lungs, in the recumbent position the ribs are more horizontal and the lungs are in relative inspiration When the subject lies on one side or leans to one side, the lower hemithorax is in collapse, its lung being relatively airless, while the upper half of the chest is enlarged and its lung is emphysematous When the subject leans now to one side, now to the other, with the breath held, one can plainly observe under the fluoroscopic screen the escape of air from the lower into the upper part of the lung This paradoxical breathing can be readily confirmed by physical examination

5 Normal respiration in the higher vertebrates depends on a drop of air pressure in the lungs with the inspiratory enlargement of the chest, so that air is admitted under atmospheric pressure, and an increased air pressure in the lungs in expiration, expelling stale air into the atmosphere The atmospheric pressure on the chest wall is overcome by the rigid ribs and by normal muscle tone In case of injury to the ribs or muscles, as after thoracoplastic operations or in rickets, the softened portions of the chest respond to atmospheric pressure in the same manner as the atmospheric air, i e., during inspiration the tissues are pressed inward, and during expiration they are pressed outward (paradoxical movement) Thus, during the same phase of respiration, the pressure may be increased in one portion of the chest and decreased in another portion, leading to an interchange of air and other fluid materials

#### PARADOXICAL BREATHING IN HEALTH

*Paradoxical Breathing in the Apices of the Lungs*—The apex of the lung, situated above the level of the anterior end of the first rib, is exposed to atmospheric pressure, the thoracic wall being deficient in bone and muscle in this region With the fall in intrapleural pressure during deep inspiration the weight of the air on the outside of the chest compresses the unprotected apex of the lung in the same manner as it presses air into the trachea With the rise of intrathoracic pressure above atmospheric pressure during forced expiration, the apex bulges out, there being no ribs or strong muscles in this region of the wall of the chest The more labored the breathing the more pronounced is this paradoxical excursion of the apex, which can be observed by direct inspection and by roentgen examination<sup>8</sup> In apical pleuritis and in

<sup>8</sup> Kreutzfuchs, S Radiological Examination of the Lung Apices, *Munchen med Wchnschr* 59 80, 1912

infiltrations associated with airlessness and bronchial occlusion, the paradoxical breathing is less pronounced or absent. In fluoroscopic examination of the chest the "normal" paradoxical behavior of the apex is looked for before tuberculosis is ruled out.

In complete unilateral pneumothorax, the air content of the apical region also diminishes in inspiration and increases in expiration, this shows that the paradoxical behavior of the apex depends on the structure of the thoracic wall rather than on the architecture of the lung.

*Paradoxical Breathing in the Mediastinal Portions of the Lungs*—During the expiratory efforts of coughing, straining and similar acts, the mediastinal portions of the lungs are inflated, the sternum and contiguous parts are elevated, and the upper four or five interspaces may bulge out (Tendeloo<sup>9</sup>). The upper three or four intercostal spaces increase in a vertical direction, as can be demonstrated by roentgenograms made during the two phases of respiration. This paradoxical behavior of the mediastinal and apical portions of the lungs is more pronounced in emphysema and is etiologically related to the production of emphysema.

CASE 1—The clinical diagnosis was chronic fibrosis and emphysema of the left lung following a gunshot wound. Roentgenograms of the chest made in inspiration and in expiration yield the following information. In expiration the right base has collapsed much better than the left, the apexes have become inflated during expiration. The first intercostal space is wider in expiration. The transverse diameter of the lungs is increased in expiration, encroaching on the mediastinal shadow. At the level of the third cartilage on the left side there is a foreign body in the anterior portion of the mediastinum, vaguely showing in inspiration, in expiration this body is well defined, owing to the inflation of the surrounding lung in expiration. On the right side the mediastinal portion of the lung is also better inflated in expiration (fig 1 A and B).

CASE 2—The clinical diagnosis was fibroid tuberculosis of the left lung of fifteen years' duration.

Stereoscopic examination of films made in inspiration shows the left lung and chest to be contracted in all directions. There are many star-shaped fibrous deposits in the upper half of the left lung. The root of the left lung is displaced upward and outward. There is a large transparent area with a convex outer border to the left of the aortic knob, it is the mediastinal portion of the right lung which has hypertrophied and has invaded the left hemithorax. Films made in expiration show the usual deflation of the bases and inflation of the apexes. The mediastinal "lung hernia" has enlarged in expiration.

The mediastinal ballooning frequently occurring in artificial pneumothorax is also more marked during the phase of expiration.

The vicarious inflation of the apical and mediastinal portions of the lungs becomes pronounced during labored breathing associated with

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<sup>9</sup> Tendeloo, N. P. Studien über die Ursachen der Lungenkrankheiten, ed. 1, Wiesbaden, J. F. Bergmann, 1902, p. 55.

severe exertion, as in track runners. The increased oxidation caused by the activity of the muscles demands labored breathing. The inspirations are deepened, and the expirations are forced and prolonged owing to the narrowed glottis, the abdominal expiratory muscles are brought into play. Air is driven with supra-atmospheric pressure from the basal into the apical and mediastinal portions of the lungs.<sup>10</sup> During the labored inspiration, air is taken in not only from the atmosphere but from the apical and mediastinal portions where the pressure may be above atmospheric. Owing to the increasing venosity of the blood, the respirations are increasingly more labored and more frequent, so that the lungs are soon overinflated, largely with stale air (*volumen pulmonum acutum*)

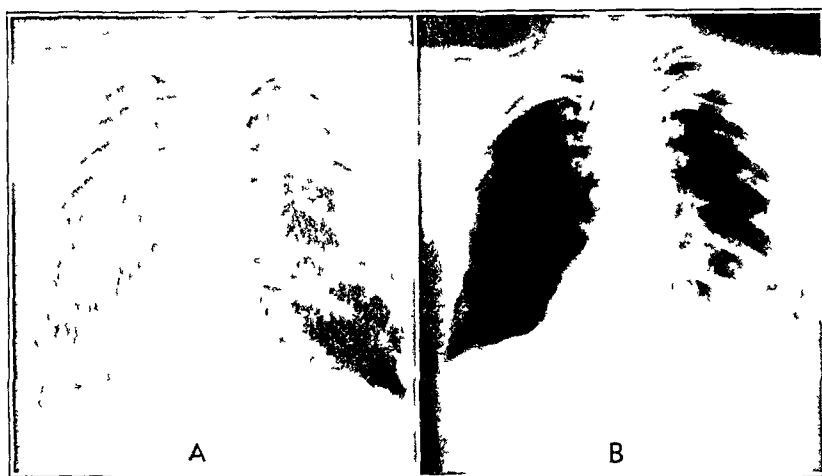


Fig 1 (case 1)—*A*, inspiration *B*, expiration. The basal portions are deflated and the apical and mediastinal portions are inflated during expiration. The foreign body in the left anterior mediastinal portion of the lung is rendered conspicuous by the inflated lung in expiration.

*The Litten Phenomenon*—In the lower lateral aspect of the chest, where the interspaces are wide and the muscle is relatively thin, there normally occurs a sinking in of the interspaces during inspiration. As the intrapleural pressure falls in inspiration, the weight of the outside air immediately presses in the soft tissues, the action of the atmospheric air through the lungs is weakened by the friction the air encounters in the long and narrow bronchi. The inspiratory retraction of the interspaces occurs simultaneously with the contraction of the diaphragm but is independent of it. The Litten phenomenon may be observed in cases of dyspnea, even if the diaphragm is paralyzed.

<sup>10</sup> FICI, cited in letter from Italian correspondent, J A M A 98 157 (Jan 9) 1932

The Harrison groove appearing in thoracic walls with soft ribs (in rickets) also develops in the same region of the chest and is due to the same factors <sup>11</sup>

#### PARADOXICAL BREATHING IN DISEASE

*Open Pneumothorax*—In this condition paradoxical breathing has been described repeatedly, both in the human subject and in the experimental animal

In the adult the lung is smaller than the cavity of the chest and it is kept stretched by atmospheric pressure into apposition with the thoracic wall, this wall is compressed by atmospheric pressure into contact with the lungs. The pressure conditions in the potential pleural space are subatmospheric. If an opening is made into the pleural cavity and air is allowed to act on the lung under atmospheric pressure the wall of the chest immediately expands, <sup>12</sup> the lung retracts from the wall and can no longer follow the respiratory movements of its hemithorax. Through the bronchial connections with the other lung, it responds to the activity of the opposite hemithorax. During each inspiration the intact lung sucks in air not only from the trachea but from the relaxed lung, during expiration it expels a portion of its air into the functionless lung. The healthy lung thus breathes a mixture of stale and fresh air. The stale air reaches the alveoli first, as the bronchus of the collapsed lung is shorter than the upper respiratory tube. The blood soon becomes venous, and cyanosis and dyspnea are marked, the respirations are forced, the expirations are prolonged and the abdominal muscles are brought into play. This is associated with narrowing of the glottis (see page 267) which means that more of the air current is diverted into the passive lung. During each violent inspiration the lung in which the pneumothorax is present collapses and the atmospheric pressure displaces the heart toward the healthy side, during the succeeding forced expiration the pressure in the healthy lung is raised considerably above atmospheric, and the heart is displaced toward the opposite side as the passive lung is ballooned out, it may be brought in contact with the wall of the chest or even be pushed through the wound. The suction force of the healthy side is thus largely spent in aspirating the mediastinum instead of in drawing in air from the trachea, conversely, some of its expiratory force is absorbed by the displacing of the mediastinum. Should the mediastinal septum be rigid, owing to inflammatory adhesions, the healthy lung will be less embarrassed in its action. Fixing of the mediastinum by manual traction relieves the dyspnea and cya-

<sup>11</sup> Gray, Henry. Anatomy, Descriptive and Surgical, new American edition from the eighteenth English edition, Philadelphia, Lea & Febiger, 1913, p. 237

<sup>12</sup> Bert, Paul, in *Leçons sur la physiologie comparée de la respiration* Paris, J. B. Baillière et fils, 1870



nosis,<sup>13</sup> conversely, pressure on the abdomen, by relaxing the mediastinal attachments, increases the distress. Producing an artificial opening in the trachea relieves the symptoms<sup>14</sup> by shortening the respiratory passages and by obviating the narrow glottis.

Placing of the subject on the wounded side causes some relief,<sup>15</sup> the mediastinum becoming fixed by its own weight (case 3, page 275).

*Hernia of the Lung*—It is now well known that in hernias of the lungs the breathing is paradoxical. Cloquet, in 1817, noted that in inspiration the hernia disappeared, in expiration it bulged out. Wahl<sup>16</sup> succeeded in demonstrating a hernia of the lung in a roentgenogram (the plate was made during straining expiration with the glottis closed).

*Asthma*—In bronchial asthma there is a spasmodic narrowing of the bronchi and glottis, more pronounced in expiration. There are increased resistance to the outflow of air and rapid accumulation of residual air. With each expiration air is driven from the basal and lateral portions of the chest into the apical and mediastinal regions.<sup>17</sup> This rebreathing is largely responsible for the respiratory distress and cyanosis.

*Emphysema*—In pulmonary emphysema there is increased residual air. The portions of the lungs affected earliest and most extensively are the apical and mediastinal regions.<sup>18</sup> It is easy to see why in bronchitis and laryngitis with chronic cough there should develop overdistention of these poorly muscled regions of the lung, by a process of paradoxical breathing. During each paroxysm of coughing air is blown into the mediastinal and apical portions of the lungs. This is also true of occupational emphysema, i. e., the emphysema following the practice of occupations entailing sustained respiratory efforts (for instance, glass blowing, singing and playing of wind instruments).

In emphysema developing in persons not engaged in strenuous occupations and without primary bronchitis it is believed that the respiratory passages are naturally longer and narrower than usual (Tendeloo<sup>19</sup>) or that there is an exaggerated narrowing of the glottis in expiration. In such persons ordinary talking and moderate manual labor may bring

13 Sauerbruch, E. F. *Chirurgie der Brustorgane*, ed. 2, Berlin, Julius Springer, 1925, vol. 1, p. 603.

14 Dwyer, J. O. *A Few Vivisection Experiments*, Loomis Laboratories, University of the City of New York, 1890, p. 53.

15 Ewald, Carl. *Ueber das Mediastinalflattern*, *Wien klin. Wchnschr.* **39** 697, 1926.

16 Wahl, Reed. *Zur Klinik und Roentgenologie der Lungenhernie*, *Fortschr. a. d. Geb. d. Rontgenstrahlen* **40** 670, 1929.

17 Hofbauer, Ludwig. *Asthma*, Berlin, Julius Springer, 1928, p. 11.

18 Lord, F. T. *Diseases of the Bronchi, Lungs and Pleura*, Philadelphia, Lea & Febiger, 1915, p. 150.

19 Tendeloo, N. P. *Studien uber die Entstehung und der Verlauf der Lungenkrankheiten*, ed. 2, Wiesbaden, J. F. Bergmann, 1931, p. 71.

about as much paradoxical breathing and as great an accumulation of residual air as occur in more normal persons only from acts associated with severe expiratory efforts

*Tuberculosis and Other Infections*—In pulmonary tuberculosis bronchiectasis pneumonia, pulmonary abscess and other infections of the lungs, there occurs an interchange of air and of infectious material between the various portions of the lungs, generally during coughing spells and during straining efforts. This paradoxical breathing is responsible for the interbronchial spread of tuberculous and other infections in the lungs and for the condition known as migratory pneumonia. During roentgen examination of patients after injections of iodized poppy seed oil 40 per cent, the spread of the oil from one lung into the other and from a lower lobe to an upper lobe bronchus has been frequently observed. During operations on the chest for tuberculosis or other infections if paradoxical breathing occurs, owing to resection of the ribs or to open pneumothorax, there is grave danger of spreading of the infection in the lungs.<sup>20</sup>

The prognosis in tuberculosis and bronchiectasis is better for persons of sedentary occupation, for the reason that these persons do not engage in strenuous muscular effort, with the concomitant paradoxical breathing (expiratory effort, with the glottis closed).

The paradoxical excursions of the wall of the chest overlying a tuberculous process can frequently be observed by inspection.<sup>21</sup> Elsewhere I have presented roentgenographic illustrations of paradoxical breathing in tuberculous cavities<sup>22</sup> and in atelectatic lungs.<sup>23</sup> Paradoxical breathing has been described as the cause of cyanosis and dyspnea in pneumonia.<sup>24</sup> The bottle-blowing exercises employed in the post-operative treatment of empyema are also of interest in this connection.

*Extensive Operations on the Wall of the Chest*—After these operations paradoxical breathing nearly always occurs, occasionally causing more disability than the condition for which the operation was performed. The paradoxical breathing is more marked if the anterior portions of the ribs are removed as in this portion of the chest the interspaces are wide and there is less muscle to protect the lung from atmospheric pressure than there is in the back of the chest. If the

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20 Davies, H. Morrison. *Surgery of the Lung*, New York, Oxford University Press, 1930, p. 33.

21 Fishberg. *Pulmonary Tuberculosis*, ed. 3, Philadelphia, Lea & Febiger, 1922, p. 308.

22 Korol, E. Atelectasis in Pulmonary Tuberculosis, *Am Rev Tuberc* **23** 505 (May) 1931.

23 Korol, E. Etiology and Mechanics of Massive Atelectasis, *Am Rev Tuberc* **24** 284 (Sept.) 1931.

24 Duken. The Significance of X-Ray Examination in Pneumonia, *Monatschr f Kinderh* **41**:174 1928.

pleura is thickened and the mediastinum is fixed, there is less respiratory distress

Following operations on the left side of the chest, the to-and-fro movement of the heart with respiration may be seen, during inspiration the heart is pulled to the right and becomes invisible, during expiration a large area of pulsation is seen to the left of the sternum (case 3) If the observer takes hold of the costal stumps and forcibly resists their collapse with inspiration the patient's respiratory distress is diminished and the paradoxical action of the underlying lung disappears, as well as the flopping of the heart. The vital capacity of the patient improves markedly when the wall of the chest is supported so that its paradoxical movement is abolished

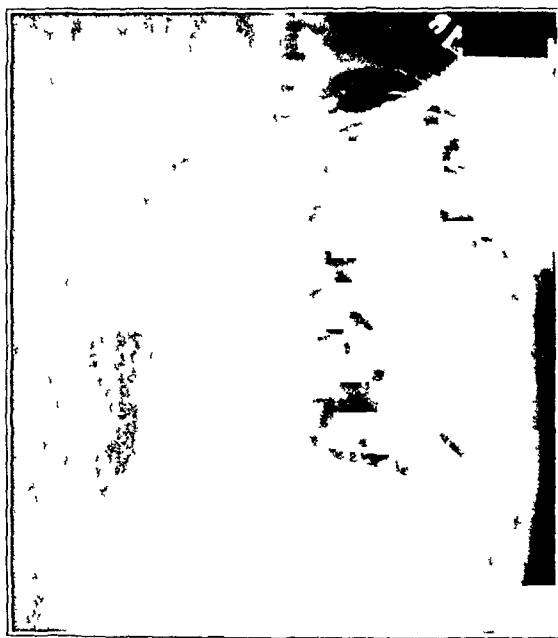


Fig 2 (case 3) —Extent of the resection of the left hemithorax. Considerable air-bearing tissue remains in the left lung

CASE 3—During the months of February and March, 1926, a man underwent an extensive thoracoplasty operation on the left side of the chest, in four stages, for the treatment of tuberculous pyopneumothorax. Portions of the upper eleven ribs were removed paravertebrally, in addition the axillary portions of the seventh, eighth, ninth and tenth ribs were resected through an incision in the anterior axillary line. The patient recovered gradually, and for two years enjoyed fair health.

In the spring of 1929, a cough developed, the patient began to lose weight, and there was marked dyspnea on exertion.

In June, 1929, the condition of the lungs was as represented in figure 2, with physical signs of cavity in the lower lobe of the right lung and tubercle bacilli in the sputum. Shortness of breath was the principal complaint. The paradoxical movement of the left lung was spectacular. The extensive thin, hairless scar in the left axilla, through which the blue lung could be seen, was deeply retracted

with each inspiration and bulged out with each expiration, fairly ballooning out with each cough and straining movement. The heart could be seen over a large area during expiration, it became invisible behind the sternum during inspiration. The larynx also moved to the right in inspiration and to the left in expiration. The patient rested on his left side continually, and decubital ulcers had developed on the stumps of three of the ribs. When the examiner took hold of the sternal stumps of the ribs and held up the thoracic wall, resisting the atmospheric pressure on the ribs in inspiration, the patient immediately volunteered the statement "This feels good. I can breathe fine this way." During this maneuver the movement of the left lung was greatly limited and the migrations of the heart and of the larynx disappeared. The vital capacity was 1,200 cc. When the sternum was held up to resist the paradoxical movement, the vital capacity rose to 1,525 cc.

There were increasing dyspnea and cyanosis. Edema of the legs appeared, and later ascites and enlargement of the liver. There were no heart murmurs. The patient did not like to be propped up on pillows, but preferred to rest on the left

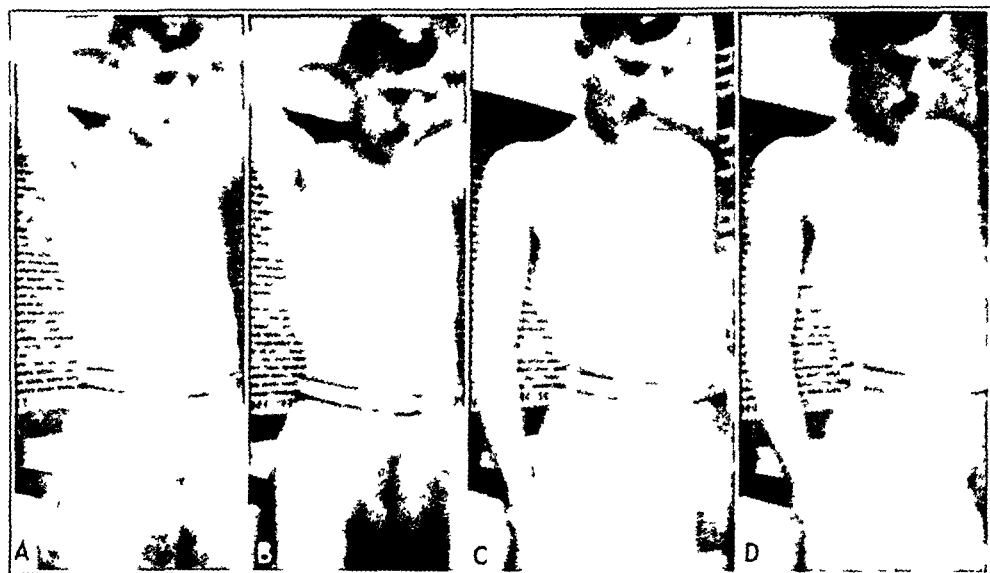


Fig 3 (case 4) —*A*, inspiration. The left side of the chest is contracted in inspiration. *B*, expiration. The left side is larger than in *A* (paradoxical breathing). *C*, inspiration with the rib stumps supported against atmospheric pressure, the left side now moves normally. *D*, in expiration the left side is now smaller than in *C* and *B*.

side (see page 272). Over two of the rib stumps the tissue sloughed away, and dead white bone was exposed. Inhalations of oxygen relieved the dyspnea and cyanosis, but just as much relief was obtained from manually pulling up on the rib stumps.

The following is an abstract of the protocol of the autopsy, dated Aug 15, 1929. There was a large amount of fluid in the peritoneal cavity. The liver was congested, and the spleen enlarged. There was much clear fluid in the pericardial cavity. The right lung showed extensive changes of tuberculosis with formation of cavities. The left lung consisted of several rather solid flat, tongue-like processes which were adherent to the operative scar, the diaphragm, the pericardium and the cupola of the pleural cavity. Air-bearing tissue was present in the anterior portions of this lung. On section this lung was described as consisting of congested areas of collapsed lung alternating with gray caseous deposits.

It will be seen that the lesions in the left lung were not healed three years following the extensive thoracoplasty. Undoubtedly the healing was disturbed by the paradoxical breathing which, during labored breathing, exceeded 20 per cent of the total (see the vital capacity figures). The air current between the two lungs probably carried the infectious material from the left into the right lung.

Death from heart failure was described in these cases by Bruns<sup>25</sup>

CASE 4—During the summer of 1929 a man underwent three operations for recurrent empyema. The eighth, ninth, tenth and eleventh ribs were resected subperiosteally, from the posterior axillary line to near the cartilaginous ends on the left side. The empyema was cured, and the patient recovered, with much deformity of the chest wall. There was a cup-shaped depression in the lower part of the left axilla which became deeper on inspiration and was nearly obliterated on expiration. When the left costal arch was supported in such a way as to resist the

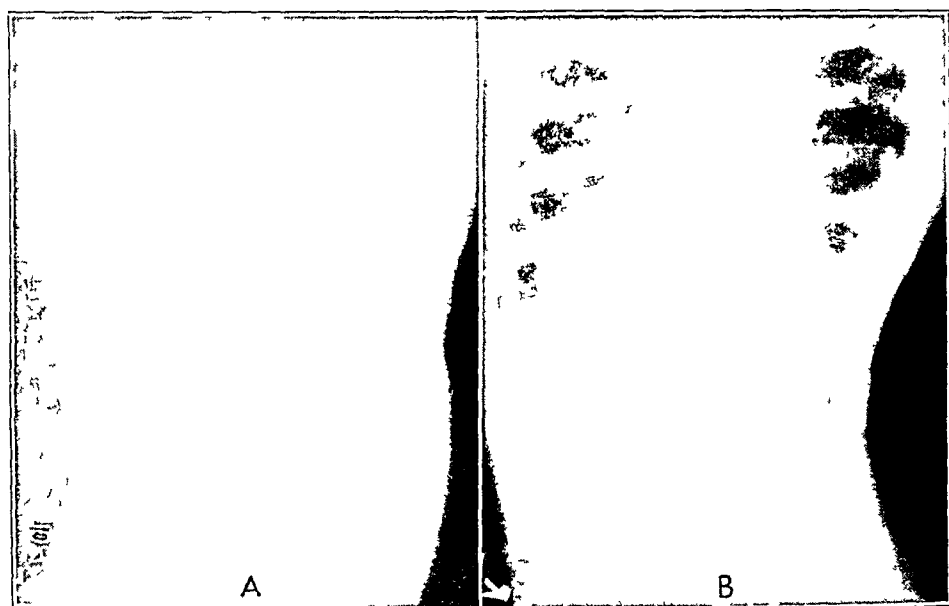


Fig 4 (case 4)—*A*, inspiration. Note collapse of the base of the left lung. *B*, expiration. The base of the left lung is inflated in this phase of respiration (paradoxical breathing).

collapse of the chest during inspiration (fig 3 *C* and *D*) the man stated that he felt better and could breathe more freely. The vital capacity on Dec 18, 1929, was 1,500 cc, and 1,900 cc with the left side of the thoracic wall supported. In October, 1931, the vital capacity was 2,700 cc, and with the left side of the thoracic wall supported, 3,100 cc. The improvement in the vital capacity and the relative decrease in the paradoxical breathing during the last examination are in part due to the regeneration of some of the resected ribs (fig 4 *A* and *B*).

CASE 5—The patient had undergone four operations for empyema. Three inches (7.6 cm) of the eighth rib was removed, and the ninth, tenth and eleventh ribs were removed from the transverse processes of the vertebrae to the cartilaginous junctions. There was a funnel-shaped depression in the posterior axillary region

<sup>25</sup> Bruns, O. Folgezustände des einseitigen Pneumothorax, Beitr z Klin d Tuberk **12** 1, 1909

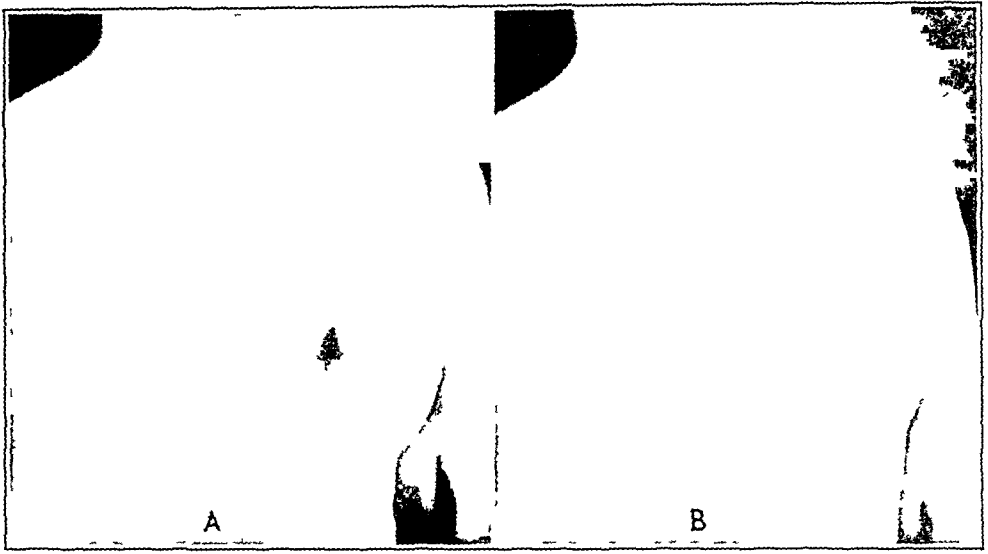


Fig 5 (case 5) —*A*, inspiration Note the contraction of the chest both in the region of the scar and in the lower axilla *B*, expiration The left side of the chest is ballooned out posteriorly, the concavity in the lateral aspect of the chest is also obliterated



Fig 6 (case 5) —*A*, inspiration *B*, expiration Note the inflation of the base of the left lung behind the liver, in the region of the resected ribs

of the chest which was deeper on inspiration and very shallow on expiration (fig 5 *A* and *B*) On auscultation, paradoxical breath sounds were heard over this portion of the chest, the inspirations were short and the expirations long and of tubular quality (fig 6 *A* and *B*)

Paradoxical breathing occurs in other congenital and acquired defects in the chest wall It has been described in fissures of the sternum,<sup>26</sup> in rickets,<sup>27</sup> in fractures of the ribs<sup>28</sup> and in paralysis of the intercostal nerves and of the nerves to the scalene muscles<sup>29</sup>

#### SUMMARY

1 Paradoxical breathing occurs in all air-breathing vertebrates It depends on the narrowing or closing of the glottis during certain respiratory acts and on the unequal pressure conditions prevailing in the different portions of the respiratory tract

2 In the amphibians and birds, paradoxical breathing, like the maintenance of residual air, serves a useful function in moistening and diluting the atmospheric air In mammals, owing to the oxygenation of the blood in all portions of their lungs, paradoxical breathing impairs the respiratory function by diminishing the vital capacity and by causing breathing of stale air

3 With an intact thoracic wall, the paradoxical breathing is limited to the apical and mediastinal portions of the lungs, these regions of the chest being poorly provided with muscle In congenital and acquired defects of the chest wall, the vicarious breathing is conspicuous in the areas of the lungs adjacent to the defects

4 During the activities of workers such as glass blowers, singers, dancers and runners, the paradoxical breathing produces acute emphysema (*volumen pulmonum acutum*) and materially curtails the efficiency of the performers

5 Paradoxical breathing is an important factor in the development of pulmonary emphysema and is largely responsible for the dyspnea and cyanosis observed in emphysema and asthma

6 Paradoxical breathing, by causing an interchange of material between the lungs, is a common cause of the interbronchial spread of infection in tuberculosis and all other diseases of the lungs

26 Virchow and Senator Case of Fissure of Sternum, *Verhandl d Berl med Gesellsch* **1** 83, 1900

27 St Engel Der Rachitistod, *Fortschr d med* **40** 543, 1922

28 Sauerbruch, E F *Chirurgie der Brustorgane*, ed 2, Berlin, Julius Springer, 1925, vol 1, p 118

29 Hoover, C F Significance of the Respiratory Movements of the Costal Margins, *Am J M Sc* **159** 633, 1920

# EPINEPHRINE

## ITS EFFECT ON THE CARDIAC MECHANISM IN EXPERIMENTAL HYPERTHYROIDISM AND HYPOTHYROIDISM

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Auricular fibrillation is the most frequent cardiac arrhythmia in hyperthyroidism, and in the paroxysmal form presents itself in varying degrees of frequency and duration. It usually disappears permanently when the hyperthyroidism is relieved<sup>1</sup>. In the patients with hyperthyroidism who have auricular fibrillation, although the state of the hyperthyroidism ostensibly may remain unchanged, the auricular fibrillation often is transitory. It seems that there may be some labile factor in these patients which in the presence of the hyperthyroid condition affects the heart so as to favor the production of the transient abnormal rhythm.

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1 Levine, S A. Unrecognized Hyperthyroidism Masked as Heart Disease, *Ann Int Med* **4** 67, 1930. Levine, S A, and Sturgis, C C. Hyperthyroidism Masked as Heart Disease, *Boston M & S J* **190** 233, 1924. Willius, F A, and Boothby, W M. Behavior of the Heart in Exophthalmic Goiter and in Adenomatous Goiter with Hyperthyroidism, *Tr A Am Physicians* **38** 137, 1923. Hamilton, B E. Heart in Toxic Thyroid States, *S Clin North America* **4** 1411, 1924. Andrus, E C. Heart Failure with Hyperthyroidism, *New York State J Med* **29** 661, 1929. Lahey, F H, and Hamilton, B E. Thyrocardiacs. Their Diagnostic Difficulties, *Surg, Gynec & Obst* **39** 10, 1924. Hamilton, B E. Clinical Notes on Hearts in Hyperthyroidism, *Boston M & S J* **186** 216, 1922. Hurxthal, L M. Auricular Fibrillation in Patients with Goiter, *Am J M Sc* **179** 507, 1930. Dunhill, T P, Fraser, F R, and Stott, A W. Auricular Fibrillation in Thyrotoxic Conditions, *Quart J Med* **17** 326, 1924. Phillips, J, and Anderson, J P. Cardiac Disturbances in Goiter, *J A M A* **89** 1380 (Oct 22) 1927. Anderson, J P. Auricular Fibrillation Associated with Hyperthyroidism, *Am J M Sc* **173** 788, 1927.



Auricular fibrillation may follow the administration of thyroid substances in man<sup>2</sup> This is not of frequent occurrence, however, and the explanation of the mechanism of auricular fibrillation in hyperthyroidism probably is not to be found only in fluctuations in the thyroxine content of the tissues, since this substance is regarded as being too stable to account for such a transitory effect<sup>3</sup>

Aub and Stein<sup>4</sup> reported a case of complete auriculoventricular heart block in which the administration of sufficient desiccated thyroid gland to raise the basal metabolic rate to 47 per cent above the normal level increased the auricular rate to 120 per minute without affecting the slow ventricular rate It may be inferred from this that the auricles are more readily affected than the ventricles by the administration of thyroid substance

There is other evidence that hyperthyroidism may predispose the auricles to unusually increased activity without being able in itself, perhaps, to initiate an abnormal rhythm Yater<sup>5</sup> demonstrated that the perfused hearts of thyroxinized rabbits beat at a much faster rate than did the hearts of normal controls Priestley and his associates<sup>6</sup> showed that the heart of one dog transplanted into the neck of another dog beat more rapidly following the administration of thyroxine to the latter Lewis and McEachern<sup>7</sup> demonstrated that both the isolated hearts and the auricles of thyroid-treated rabbits continued to beat more rapidly than similar preparations from normal animals Furthermore, isolated hearts and auricles from thyroxinized or thyroid-fed rabbits responded to epinephrine with greater absolute increases in rate and amplitude than did those of normal controls The results of the work of Lutolf<sup>8</sup> are in agreement with this

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2 Wedd, A M Auricular Fibrillation Produced by Thyroid Medication, *Clifton M Bull* **17** 57, 1931 Gram, H C Perpetual Arrhythmia After Use of Thyroidine, *Hospitalist* **72** 381, 1929 Hyman, H T Electrocardiographic Record of a Paroxysmal Cardiac Irregularity as a Manifestation of Thyroid Administration, *Am Heart J* **5** 383, 1930

3 Kendall, E C Thyroxine, *Am Chem Soc Monog Ser* no 47, New York, The Chemical Catalog Company, 1929, chap 21

4 Aub, J C, and Stern, N S The Influence of Large Doses of Thyroid Extract on the Total Metabolism and Heart in a Case of Heart Block, *Arch Int Med* **21** 130 (Jan) 1918

5 Yater, W M Thyroxin Tachycardia in Perfused Hearts of Thyroxinized Rabbits, *Am J Physiol* **98** 338, 1931

6 Priestley, J T, Markowitz, J, and Mann, F C The Tachycardia of Experimental Hyperthyroidism, *Am J Physiol* **98** 357, 1931

7 Lewis, J K, and McEachern, D Persistence of an Accelerated Rate in Isolated Hearts and Isolated Auricles of Thyrotoxic Rabbits, *Bull Johns Hopkins Hosp* **48** 228, 1931

8 Lutolf, W Investigations on the Enhancement of the Action of Adrenalin on the Surviving Mammalian Heart by Means of Thyroxin, *Ztschr f Biol* **90** 334, 1930

Cardiac hypertrophy in experimental hyperthyroidism has been reported by numerous writers.<sup>9</sup> A difference of opinion exists as to whether or not there are any histologic changes in the heart following the production of hyperthyroidism in animals. Farrant,<sup>10</sup> Hashimoto,<sup>11</sup> Goodpasture<sup>12</sup> and Takane<sup>13</sup> reported various microscopic pathologic changes in the heart muscle in experimental hyperthyroidism. Cameron and Carmichael<sup>14</sup> on the other hand, found no histologic abnormalities in the hearts of animals with hyperthyroidism. Rake and McEachern,<sup>14</sup> in a carefully controlled study, reported that in the absence of infection the hearts of guinea-pigs and rabbits with hyperthyroidism showed no significant microscopic changes. The same authors studied the hearts of 27 patients dying of hyperthyroidism,<sup>15</sup> compared with 150 "suitable" controls, and concluded that there were no consistent significant histologic changes.

The reports of Lewis and McEachern<sup>7</sup> and Lutolf<sup>8</sup> indicate that there is an increased reaction of the hearts of animals with hyperthyroidism to epinephrine. Schermann<sup>16</sup> demonstrated, moreover, that hearts isolated from normal rabbits were fifty times more susceptible to the action of epinephrine than hearts isolated from thyroidectomized

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9 (a) Iscovesco, H. The Physiological Activity of a Thyroid Extract, *Compt rend Soc de biol* **75** 361, 1913. (b) Hoskins, E. R. Growth of the Body and Organs of the Albino Rat as Affected by Feeding Various Ductless Glands, *J Exper Zool* **21** 295, 1916. (c) Herring, P. T. Action of Thyroid upon the Growth of the Body and Organs of the White Rat, *Quart J Exper Physiol* **11** 231, 1917. (d) Hewitt, J. A. Effect of Administration of Small Amounts of Thyroid Gland on the Size and Weight of Certain Organs in the Male White Rat, *Quart J Exper Physiol* **12** 347, 1918-1920. (e) Cameron, A. T., and Carmichael, J. Effect of Thyroxine on the Growth in White Rats and in Rabbits, *I Biol Chem* **46** 35, 1921. (f) Comparative Effects of Thyroid and of Iodid Feeding on Growth in White Rats and Rabbits, *J Physiol* **54** 1-14, 1920-1921. (g) Simonds, J. P., and Brandes, W. W. Size of the Heart in Experimental Hyperthyroidism, *Arch Int Med* **45** 503 (April) 1930.

10 Farrant, R. Hyperthyroidism. Its Experimental Production in Animals, *Brit M J* **2** 1363, 1913.

11 Hashimoto, H. Heart in Experimental Hyperthyroidism, *Endocrinology* **5** 579, 1921.

12 Goodpasture, E. W. Influence of Thyroid Products on the Production of Myocardial Necrosis, *J Exper Med* **34** 407, 1921.

13 Takane, K. Experimental Acute Myocarditis Following Thyroidine and Iodin Salts, *Virchows Arch f path Anat* **259** 736, 1926.

14 Rake, G., and McEachern, D. Experimental Hyperthyroidism and Its Effect upon the Myocardium in Guinea Pigs and Rabbits, *J Exper Med* **54** 23, 1931.

15 McEachern, D., and Rake, G. Study of the Morbid Anatomy of Hearts from Patients Dying with Hyperthyroidism, *Bull Johns Hopkins Hosp* **48** 273, 1931.

16 Schermann, S. J. Reaction of Isolated Hearts of Thyroidectomized Animals to Adrenalin, *Arch f exper Path u Pharmacol* **126** 10, 1927.

animals Andrus<sup>17</sup> showed that following the administration of epinephrine intravenously there is a definite increase in the rate of intra-auricular conduction time in normal cats and dogs. This occurred with doses of from 0.25 to 1 cc of a 1:50,000 solution. Allen found that the injection of even larger doses of epinephrine than these caused no arrhythmias in normal rabbits and dogs.<sup>18</sup>

Cowan, however, stated that auricular fibrillation may be produced by the injection of epinephrine into laboratory animals in either the intact state<sup>19</sup> or in a heart perfusion preparation.<sup>20</sup> Otto<sup>21</sup> wrote that "practically every known type of arrhythmia," including auricular fibrillation, may occur in normal animals following the injection of epinephrine. Neither of these authors quoted any experimental evidence in support of these statements.

Premature auricular and ventricular beats and complete dissociation of the auricles and ventricles were reported following the injection of epinephrine into normal animals<sup>22</sup> and man.<sup>23</sup> Ventricular fibrillation following the injection of epinephrine into normal cats under chloroform anesthesia was reported by Levy.<sup>24</sup>

Four cases have been reported<sup>25</sup> in which transient auricular fibrillation occurred in patients following the injection of epinephrine. In one of these patients<sup>21</sup> spontaneous auricular fibrillation had appeared

17 Andrus, E. C. Action of the Sympathetic upon the Excitatory Process in the Mammalian Heart, *J. Exper. Med.* **45** 1017, 1927.

18 Allen, W. F. Bigeminal Pulse in Rabbits, *Am. J. Physiol.* **95** 190, 1930.

19 Cowan, J. Causes of Auricular Fibrillation, *Quart. J. Med.* **22** 237, 1929.

20 Cowan, J., and Ritchie, W. T. Diseases of the Heart, London, Edward Arnold & Co., 1922, p. 175.

21 Otto, H. L. Action of Epinephrine on the Cardiac Rhythm, *J. Lab. & Clin. Med.* **13** 70, 1927.

22 Rothberger, J. C., and Winterberg, H. Experimental Production of Ventricular Extra-Systoles, *Arch. f. d. ges. Physiol.* **142** 461, 1911. Kahn, R. H. Electrocardiographic Changes Following Adrenalin, *Arch. f. d. ges. Physiol.* **129** 291, 1909.

23 (a) Danielopolu, D., and Danulesco, V. Paroxysmal Ectopic Tachycardia in Man Produced by Adrenalin, *Ann. de med.* **10** 1, 1921. (b) Clough, H. D. Effect of Epinephrine on Electrocardiogram of Patients with Irritable Hearts, *Arch. Int. Med.* **24** 284, 1919. (c) DeGraff, A., and Weiss, S. Observations on the Extrinsic Nervous Control of the Auricles and Ventricles in Complete A-V Block in Man, *J. Clin. Investigation* **2** 227, 1926. (d) Otto, H. L., and Gold, H. Persistent Premature Contractions, *Arch. Int. Med.* **38** 186 (Aug.) 1926. (e) Hume, W. E. The Action of Adrenalin Chloride on the Human Heart, *Quart. J. Med.* **21** 459, 1928.

24 Levy, A. G. The Exciting Causes of Ventricular Fibrillation in Animals under Chloroform Anesthesia, *Heart* **4** 319, 1912-1913.

25 (a) Smith, F. M., and Moody, W. B. Induction of Premature Contractions and Auricular Fibrillation by Forced Breathing, *Arch. Int. Med.* **32** 192 (Aug.) 1923. (b) Otto<sup>21</sup>. (c) Hume<sup>23e</sup>.

previously, and in another<sup>25</sup> auricular fibrillation previously had followed forced deep breathing. In none of these four cases was specific evidence for or against hyperthyroidism mentioned. Tompkins, Sturgis and Wearn<sup>26</sup> injected 0.5 cc of a 1:1,000 solution of epinephrine into three patients with hyperthyroidism according to the method of Goetsch<sup>27</sup>. The authors followed the changes in blood pressure and pulse rate, but did not mention the presence or absence of arrhythmia.

As hyperthyroidism increases the activity of the heart, especially that of the auricles, and has been shown to enhance the cardiac response to epinephrine, it was decided to try the effect of epinephrine on the rhythm of the intact hearts of normal animals and of those with hyperthyroidism and hypothyroidism.

#### METHOD OF EXPERIMENTATION

A Benedict portable respiration machine<sup>28</sup> was used to determine the oxygen consumption of the rabbits. It had an outside electric blower and was attached to a water-sealed animal chamber. The apparatus was tested twice weekly to demonstrate the absence of leaks. Wilson's soda lime was used for carbon dioxide absorption. A water vapor absorbent was not used.

The rabbits were kept on a diet of oats, alfalfa hay and lettuce. Their average weight was 2,400 Gm. They were made to fast from sixteen to eighteen hours before each determination of metabolism. The oxygen consumption was noted for successive ten minute periods until three or four consecutive checks were obtained. The temperature readings of the oxygen reservoir were recorded every ten minutes, and the barometric pressure was read at the beginning of each determination. The determinations of the basal metabolic rate on normal animals agreed with the results of other experimenters<sup>29</sup>.

Seventeen rabbits were used and were divided into three groups. Hyperthyroidism was produced in the first group of ten animals. Four were given desiccated thyroid gland, 0.260 Gm (4 grains) daily by mouth. In three others hyperthyroidism was induced in a similar way. Then thyroid feeding was discontinued until the basal metabolic rate became normal. It was then resumed until a second state of hyperthyroidism was obtained. The remaining two animals were given thyroxine, 0.001 Gm ( $\frac{1}{100}$  grain) daily subcutaneously for three days. The second group consisted of three rabbits, they were thyroidectomized, and their basal metabolic rates were followed until a definite hypothyroidism developed.

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26 Tompkins, E. H., Sturgis, C. C., and Wearn, J. T. The Effects of Epinephrine on the Basal Metabolism in Soldiers with "Irritable Heart," in Hyperthyroidism and in Normal Men, *Arch. Int. Med.* **24**: 269 (Sept.) 1919.

27 Goetsch, E. *Diagnosis of Thyroid Disorders*, New York State J. Med. **18**: 259, 1918.

28 Benedict, F. G. *A Portable Respiration Apparatus for Clinical Use*, Boston M. & S. J. **178**: 667, 1918.

29 Krogh, A. *Respiratory Exchange in Animals and Man*, New York, Longmans, Green & Co., 1916, p. 141. Webster, B., Clawson, T. A., and Chesney, A. M. Heat Production in Goitrous and Non-Goitrous Animals, *Bull. Johns Hopkins Hosp.* **43**: 278, 1928. Lund, C. C., and Benedict, E. B. Influence of the Thyroid Gland on the Action of Morphine, *New England J. Med.* **201**: 345, 1929.

Autopsy was performed on one five months after operation, and gross findings in agreement with those reported by Tatum<sup>30</sup> in myxedematous rabbits were found. The third group was composed of five normal rabbits which were used as controls.

Epinephrine was injected intravenously into each animal of these groups. Electrocardiograms were taken immediately before, during and after the injections and until all the effects produced by the injection had disappeared permanently. Any changes that occurred disappeared permanently within from ten to fifteen minutes after the injection. In three of the animals of the first group, injections and tracings were made during the first period of hyperthyroidism, in the ensuing normal state and in the second period of hyperthyroidism.

Forty-five experiments were made on these seventeen rabbits. The amounts of epinephrine injected varied from 0.5 cc of 1:1,000 to 1 cc of 1:1,000,000 dilutions. Epinephrine was not administered on the basis of a given amount per kilogram of body weight, because of the close similarity of the weights of the animals to the average weight of the group (2,400 Gm). The differences in weight that did exist did not seem to play a part in the reactions of the animals. Orientation

*Effect on the Cardiac Rhythm of the Injection of Epinephrine into Normal Rabbits and into Those with Hyperthyroidism and Hypothyroidism\**

No Animals	No Experiments	Average BMR, per Cent	Dilutions of Epinephrine	Dose, Cc	PVT	AT	ES	Ch Q R S	NR	Slw	VF	Death
5	20	+75	1:100,000	1.0	20	5	2	1	7			
3	3	-34	1:100,000	1.0						3		
6	6	± 0	1:100,000	1.0						6		
4	5	+82	1:1,000	0.1 to 0.5	3	2		1			3	3
4	4	± 0	1:1,000	0.1 to 0.5	3		2	1	1	1	1	1

\* Abbreviations in the table represent the following: BMR, basal metabolic rate (per cent of normal); PVT, paroxysmal ventricular tachycardia; AF, auricular fibrillation; ES, extrasystoles; Ch Q R S, changing form of Q R S complex; NR, nodal rhythm; Slw, slowing of the rate; VF, ventricular fibrillation.

Note the frequency of auricular fibrillation in the animals with hyperthyroidism and its absence in the normal animals and those with hypothyroidism.

experiments showed that the dose most suitable to compare the reactions of normal animals and of those with hyperthyroidism and hypothyroidism was 1 cc of 1:100,000 dilution of epinephrine (0.01 mg). Doses smaller than this did not produce consistent electrocardiographic changes. Solutions of epinephrine hydrochloride were made by diluting epinephrine (1:1,000) with Ringer's solution. This diluent when injected alone produced no changes in the electrocardiogram.

## RESULTS

Twenty injections of 1 cc of 1:100,000 epinephrine made into five rabbits with hyperthyroidism produced the following electrocardiographic effects: paroxysmal ventricular tachycardia, nodal rhythm, probable auricular fibrillation and ectopic beats (table). Each injection of this dose of epinephrine was followed promptly by a paroxysm of ventricular tachycardia (fig 1 A). Transient auricular fibrillation (fig 1 B) occurred after four injections, appearing immediately or within a half-minute after the ventricular tachycardia had disappeared.

<sup>30</sup> Tatum, A. L. Morphological Studies in Experimental Cretinism, J. Exper. Med. 17: 636, 1913.

In three other instances, changes consistent with auricular fibrillation, although not quite as definite as those mentioned, were noted (fig 1 C). The electrocardiographic changes that were interpreted as indicative of auricular fibrillation were (1) grossly irregular ventricular rhythm, (2) absence of the auricular (P) waves and (3) the presence of fibril-

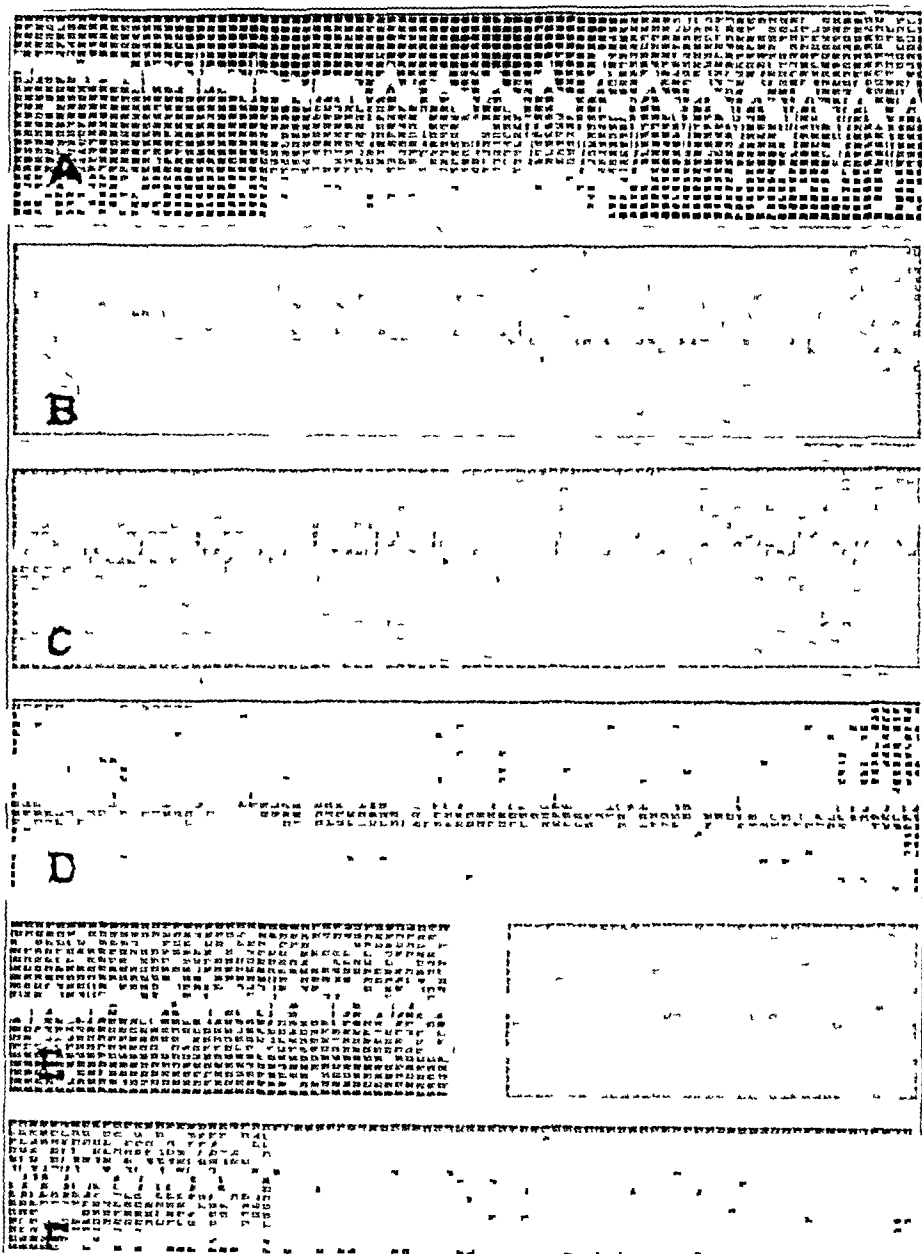


Fig 1—A shows development of a characteristic attack of paroxysmal ventricular tachycardia in a rabbit with hyperthyroidism following 1 cc of 1:100,000 epinephrine intravenously. B shows auricular fibrillation produced by 1 cc of 1:100,000 epinephrine in a rabbit with hyperthyroidism. C is similar to B, except that the curves are suggestive of auricular fibrillation. D, same as A, except the mechanism here is nodal rhythm alternating with normal rhythm. E shows the slowing following 1 cc of 1:100,000 epinephrine in a normal rabbit or one with hypothyroidism. F shows ventricular fibrillation following a large dose of epinephrine (0.25 cc of 1:1,000) in a rabbit with hyperthyroidism.

lary (ft) waves In two animals (in one of which an irregularity corresponding to the foregoing criteria of auricular fibrillation had twice developed) the injections of epinephrine (1 cc of 1 100,000) were followed in the usual way by paroxysmal ventricular tachycardia, but after this the electrocardiogram showed a slow, regular ventricular action and absence of the auricular (P) waves We have interpreted this as auriculoventricular nodal rhythm (fig 1 *D*), it occurred seven times in these two rabbits with hyperthyroidism

The dose (1 cc of 1 100,000) given to three normal rabbits, three rabbits with hypothyroidism and three rabbits which previously had had hyperthyroidism but now had a normal basal metabolic rate was followed in each case by only a transient slowing of the rate without irregularity (fig 1 *E*) This appeared within a few seconds after the injection and continued for about one to one and a half minutes The rate then returned to normal (table)

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FIG. 2—The development of auricular fibrillation in a dog with hyperthyroidism about forty-five seconds after the intravenous injection of 0.5 cc of 1 10,000 epinephrine

Larger doses of epinephrine were given to both normal rabbits and those with hyperthyroidism Five injections (with from 0.1 to 0.5 cc of 1 1,000 dilution) were given to four rabbits with hyperthyroidism In three of the animals ventricular tachycardia developed immediately after the injections This was followed by ventricular fibrillation (fig 1 *F*) and death The fourth animal did not die and injection was made twice Following one injection in this rabbit only changing Q-R-S complexes developed, and after the second injection, several days later, transient auricular fibrillation occurred (table) Similarly large doses (from 0.1 to 0.5 cc of 1 1,000) were given also to four normal rabbits In three paroxysmal ventricular tachycardia developed promptly, in the fourth numerous ectopic ventricular beats but no tachycardia The latter animal, however, received the smallest dose (0.1 cc) All these rabbits recovered except one in which ventricular fibrillation developed This animal was given the largest dose (0.5 cc, table)

## COMMENT

The frequent but by no means constant coexistence of transient auricular fibrillation and hyperthyroidism clinically led us to suspect that some factor in addition to the hyperthyroidism might be responsible for the cardiac arrhythmia. It is obvious that the heart structure must be the same at the moment auricular fibrillation develops as it was the moment before when the heart was beating regularly. One can readily picture a sudden change in the functional or nervous properties of the heart which could produce alterations in rhythm. The clinical observation that in some patients with hyperthyroidism paroxysms of auricular fibrillation develop immediately following a sudden emotional strain suggested the possibility that the suprarenals may be playing a rôle in the production of auricular fibrillation when hyperthyroidism is present. Furthermore, from experimental data it was shown that the cardiac response to epinephrine is greater in the presence of hyperthyroidism.<sup>7, 8</sup> Therefore it was decided to study the effect of epinephrine on the cardiac rhythm in animals with hyperthyroidism and to control these experiments by observations on normal animals as well as on those with hypothyroidism. The experiments indicate that the smallest doses of epinephrine which are followed by various cardiac arrhythmias in animals with hyperthyroidism produce no change in the cardiac rhythm of normal animals. Doses of epinephrine large enough to cause significant arrhythmias consistently in normal animals usually caused death when given to animals with hyperthyroidism. Paroxysmal ventricular tachycardia was the most frequent arrhythmia following the injection of epinephrine into normal animals or those with hyperthyroidism, provided enough epinephrine was given to produce any significant change. Electrocardiographic changes consistent with auricular fibrillation occurred after seven of the twenty-five injections (28 per cent) into rabbits with hyperthyroidism.

It is interesting to compare the results of injections of epinephrine in some of the rabbits of group 1 during the hyperthyroid, the ensuing normal and the second hyperthyroid states. In the hyperthyroid state these animals exhibited a marked cardiac response to small doses of epinephrine, as evidenced by paroxysmal ventricular tachycardia, extrasystoles, auricular fibrillation and nodal rhythm. After the basal metabolic rate had dropped to normal, they reacted to the same dose of epinephrine with slowing of the rate only, just as the three normal rabbits and the three with hypothyroidism reacted. This demonstrates the transient effect of experimental hyperthyroidism on the hearts of this group of animals as evidenced by the reaction to epinephrine. When hyperthyroidism was again developed, their response to epinephrine was similar to that in the first experiment.



Injectations of epinephrine in increasing amounts were given to normal rabbits until a lethal dose was administered, but tracings indicative of auricular fibrillation never were obtained in this group. The dose of epinephrine necessary to kill a normal rabbit apparently was from two to five times greater than that required for a lethal result in rabbits with hyperthyroidism. Petzetakis<sup>31</sup> reported the occurrence of auricular fibrillation following lethal doses of epinephrine to normal rabbits. The amounts that he gave varied from 1 to 1.5 mg per kilogram of body weight. These doses were about six to seven times greater per kilogram than the largest lethal dose used in our experiments. In his experiments sublethal doses given to normal animals did not cause auricular fibrillation.

The difficulty of interpreting electrocardiograms of rabbits is well recognized because of the small size of the complexes and the normally rapid rate, which is increased in hyperthyroidism. It is possible that an animal which has a heart larger than that of a rabbit would be preferable for the study of cardiac arrhythmias. Accordingly, trial experiments were made on two large dogs. Each weighed 22 Kg. One was fed from 10 to 15 Gm of desiccated thyroid gland daily for three weeks, and the other was given 10 mg of thyroxine subcutaneously daily for three days. Following this, electrocardiographic tracings were taken before, during and after the giving of varying amounts of epinephrine. All injections of epinephrine were given intravenously.

It was found that the largest dose of epinephrine which would not cause arrhythmia in these dogs when they were normal was 0.5 of 1:1,000. After hyperthyroidism was produced, however, the same dose consistently produced premature ventricular beats and questionable sino-auricular block in both dogs. In the second dog on one occasion auricular fibrillation was produced by this dose (fig. 2). The state of the hyperthyroidism was evidenced by tachycardia, slight diarrhea and moderate loss of weight. The basal metabolic rates were not determined. When thyroxine was used to induce hyperthyroidism, the injections of epinephrine were made on the second, third and fourth days after the last administration of thyroxine. The administration of thyroid was discontinued for two months in both dogs. Then each was given 5 mg of thyroxine subcutaneously daily for three days, and injections of epinephrine were made in the same way as described previously. This time no auricular fibrillation was noted, otherwise the cardiac reactions of the dogs according to the electrocardiographic tracings, were the same as when they had hyperthyroidism for the first time.

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31 Petzetakis, M. Electrocardiographic Study of the Action of Adrenalin on the Cardiac Rhythm of the Rabbit, *J de physiol et de path gen* 29 428, 1931

## CONCLUSIONS

1 The effect of epinephrine on the cardiac mechanism in normal rabbits and in those with hyperthyroidism and hypothyroidism was studied with the electrocardiograph

2 The hearts of rabbits with hyperthyroidism were more susceptible to the action of epinephrine than were the hearts of normal animals and those with hypothyroidism

3 Auricular fibrillation was produced in rabbits with hyperthyroidism and in one dog with hyperthyroidism by amounts of epinephrine insufficient to affect the cardiac rhythm of these animals when they did not have hyperthyroidism

4 Paroxysmal ventricular tachycardia was produced in rabbits with hyperthyroidism by doses of epinephrine too small to alter the normal cardiac rhythm of normal animals or those with hypothyroidism

5 The minimal lethal dose of epinephrine in rabbits was diminished in the hyperthyroid state

# SYNDROME OF PNEUMOCOCCIC BRONCHIAL OBSTRUCTION

EXPERIMENTAL PRODUCTION OF ATELECTASIS OR LOBAR PNEUMONIA  
WITH HUMAN PNEUMONIC SPUTUM, SUGGESTION FOR PRE-  
VENTIVE AND THERAPEUTIC TREATMENT

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It is only within relatively recent years that the importance of bronchial obstruction for the production of a wide variety of pulmonary diseases has come to be more generally recognized. True, in frank foreign body obstruction of a bronchus, it has been known that absorption of the air and atelectasis can ensue. Aside from advancing the therapy of this type of obstruction, Chevalier Jackson was the first to recognize atelectasis as a symptom of bronchial obstruction by diphtheritic membranes and to cure so-called diphtheritic pneumonia by bronchoscopic aspiration. William Pasteur in 1890 had noticed the frequent occurrence of atelectasis ("massive collapse") of the lung in diphtheria, but ascribed it etiologically to paralysis of the diaphragm, which he thought could bring about the airless state of the lung. In Pasteur's cases the high diaphragm was the result and not the cause of the condition, for it is well known today that paralysis of the diaphragm cannot produce atelectasis.

Experimentally, it was shown by Traube in 1844 that mechanical occlusion of a bronchus by shot or gum arabic could produce atelectasis. Mendelssohn in 1846 demonstrated, in addition, that open pneumothorax could result in the same condition, in a recent paper we have explained this on the basis of the complete collapse and occlusion of bronchioles that occur following pneumothorax and the absorption of alveolar gases by the blood in the same manner as if a bronchus were completely obstructed. Lichtheim in 1879 proved beyond doubt the importance of complete bronchial obstruction and of the integrity of the pulmonary circulation for the absorption of gases and the production of

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an anless state of the lung. He was the first to demonstrate the relative speeds of absorption of carbon dioxide, oxygen and nitrogen from the lung, although his actual figures are slightly different from the more refined determinations we have recently made.

Clinically Legendre and Bailly in 1844 noticed the frequent coincidence of atelectasis and bronchitis in children and considered bronchial obstruction with secretions as playing a part in its causation. The true mechanism of its production was however, little understood by these authors. Gairdner in 1851 also noticed the occurrence of atelectasis with bronchitis and ascribed it to a mechanical ball-valve bronchial obstruction by mucus on inspiration—an explanation which supposes a perfect functioning of mucus as a valve, they failed to understand, however, that even by such a process complete removal of alveolar air is impossible without the aid of the pulmonary circulation. Barthels in 1860 observed mucus obstruction of the corresponding bronchi at postmortem examination in cases of atelectasis including those occurring in patients with diphtheria. He remarked that Vinchow first called attention to the necessity of the pulmonary circulation for absorbing alveolar air after complete bronchial obstruction and concurred in the view that mechanical expulsion of air, alone, could not satisfactorily explain the production of atelectasis. Pearson-Irvine in 1876 had already reported a case of atelectasis complicating diphtheria, thus antedating William Pasteur's reports by a few years. Along with his own cases, Pasteur later reported a case of Samuel West's, in which atelectasis "followed the obstruction of a main bronchus by a cast."

We recently performed a thoracoplasty on a white woman, 27 years old, with tuberculosis of the left lung at the Metropolitan Hospital, New York. Twenty hours after operation typical atelectasis developed, and the patient was moribund. Under the influence of hyperventilation with oxygen and carbon dioxide, a profuse expectoration of mucus was started, and this mucus when put in water assumed the typical form of a large bronchial cast. The patient recovered. Bacteriologic examination showed the presence of pneumococci of type IV in almost pure culture.

From the foregoing paragraphs it is readily seen that the groundwork for demonstrating the rôle of bronchial obstruction in at least one phase of pulmonary disease (atelectasis) was thus laid a good many years ago. It is nevertheless probably true that the "literary bombardments" of William Pasteur, who reported a series of cases in 1890, 1908, 1910 and 1914, were a decided factor in impressing "massive collapse" (atelectasis), as an entity, on the clinical consciousness. But if this clinical recognition was becoming established, the ideas on the pathogenesis of atelectasis were becoming more and more confused, not to say fanciful until only very recently. It seems pitiful that the papers of Traube and

Mendelssohn and the monumental work of Lichtheim should have been so completely overlooked, forgotten or ignored as to give rise to the heated controversy on the pathogenesis of "massive collapse" to which Pasteur, Rose-Bradford, Briscoe, Bergamini and Shephard, Scott and a host of others have contributed. This phase of the subject forms an interesting chapter, for the details of which the reader is referred to our other papers. In these are discussed at length the various theories of pathogenesis, paralysis of the diaphragm, "bronchomotor reflex," bronchial constriction, mechanical expulsion of air, "angioneurotic edema," "hydremic plethora," etc.—a formidable list of barriers to a true understanding of the pathogenesis and therapy of atelectasis, which, we believe, have finally been removed with the aid of sound physico-chemical and physiologic principles.

According to our findings there is only one final mechanism in the production of atelectasis—complete bronchial obstruction and absorption of the gases in the alveoli by the circulating blood according to definite laws. A ball-valve obstructing mechanism may modify the speed of the production of atelectasis, but complete absorption of alveolar air and atelectasis cannot ensue without complete bronchial obstruction. The rate of production of atelectasis is dependent on the particular gases or vapors that happen to be in the lung. When bronchial obstruction is *complete* and the *pulmonary circulation normal*, atelectasis occurs, without these two factors atelectasis cannot occur. There are many contributory factors in atelectasis, such as the absence of cough, splinting of the chest, edema of the bronchial mucosa and viscid sputum, but there is only one mechanism of its production—bronchial obstruction. The truth of this contention is especially evident in postnatal atelectasis, in which the absence of aeration of the lung and the persistence of "fetal lung" can be ascribed to no other cause than bronchial or bronchiolar obstruction. The cause of this obstruction has been repeatedly found to be amniotic fluid and dermal cells (Coryllos, Henderson). It is of interest to notice here the importance of this bronchial obstruction to subsequent development of lobar pneumonia or bronchopneumonia in these new-born infants. In fact, Cruickshank in a special report of the Medical Research Council on the causes of neonatal death gave the results of 800 autopsies, in 179 of the cases the condition causing death was pneumonia, so that "the frequency of pneumonia was practically 23 per hundred deaths, many of these cases which have been placed in the group of 'death from infection' were predisposed to these infections by the effect of birth asphyxia" due to bronchial obstruction.

The mechanism of lobular or patchy atelectasis we consider as likewise dependent on complete occlusion of lobular bronchi, with this additional requisite that absorption of air from a lobule presupposes sufficient inflammation of the parenchyma to prevent the physiologic

interchange of gases between lobules, so that the gases within a lobule can be completely absorbed. Van Allen and Adams showed that this interchange normally exists and prevents lobular atelectasis, even with complete bronchial obstruction. We do not agree with them, however, on the necessity for "alveolar pores," the gaseous exchange between alveoli through the interalveolar septums, which are normally permeable to gases, being physiologic. The same mechanism of production of lobular atelectasis obtains as for lobar atelectasis, but we cannot agree with Diaz that lobar atelectasis always starts as patchy atelectasis, because on the latter supposition we could not explain the sudden onset of the disease and its lobar distribution from the start, as shown by roentgen and physical signs. We do not deny, however, that originally patchy areas may, by confluence, simulate a lobar distribution.

In this country the first true correlation of experimental and clinical data was established by Jackson, who cured diphtheritic atelectasis by bronchoscopic aspiration of membranes (1925). Subsequently, Harrington in 1927 successfully treated a patient with postoperative atelectasis ("drowned lung") by seventeen successive bronchoscopies in which large volumes (several hundred cubic centimeters) of thin, serous exudate were aspirated from the lung. In the same year Hearn and Cleif reported the bronchoscopic aspiration of thick purulent mucus from the trachea and bronchi in a case of postoperative atelectasis.

In recent papers Jacobaeus and Westermark reported the occurrence of atelectasis in typical bronchial obstruction after hemorrhage in pulmonary tuberculosis, and also in obstruction of the bronchi by granulation tissue. Wilson reported massive atelectasis after pulmonary hemorrhage in pulmonary tuberculosis. Bronchial casts of clotted blood and fibrin were coughed up, and the lung was almost normal in twelve days.

Mullet, Overholt and Pendergrass in a paper on postoperative pulmonary hypoventilation reported a high position of the diaphragm. The decrease of the bronchial air currents, in their opinion, is conducive to stagnation of bronchial secretions and consequent bronchial obstruction. Packard reported five nonsurgical cases of tuberculosis, with symptoms and signs of atelectasis, in which there was chronic fibrous pulmonary tuberculosis. One case was complicated by pulmonary carcinoma and one by a benign tumor of the lung. He concluded that fibrous occlusion of the bronchi or complete obstruction by bronchial glandular enlargement was the cause of the atelectasis. Jones reported two cases of atelectasis occurring without previous operation. One was in a boy of 8, who fractured his right humerus in an automobile accident. Three days later massive atelectasis of the left lung was noted. The other was in a girl, 18 months old, in whom in the course of measles a left-sided atelectasis developed.

The first successful bronchoscopic aspiration in lobar pneumonia (performed on a boy 19 years old, at the New York Hospital) was reported by one of us (Coryllos) in July, 1929, in a paper concerning a series of nine bronchoscopic aspirations in lobar pneumonia, performed with the collaboration of Dr L A Conner, Dr Alexander Lambert and Dr J Keenan Mainzer in 1931 reported two cases of lobar pneumonia with the physical and roentgen signs of atelectasis.

The first occurred in a man, 30 years old, who three days prior to admission had had a chill. On admission his temperature was 103 F, his pulse rate, 120, and his respiration rate, 30. Roentgen examination showed complete right pneumonia with dextrocardia. Bronchoscopy was performed. The mucosa of the trachea and right bronchus was deep red. Three centimeters below the carina a gelatinous mass was noted in the right main bronchus which, when removed, amounted to 18 cc. Instantaneous relief of dyspnea ensued. This material contained many pneumococci and a few streptococci and staphylococci. The same evening the temperature was 98 F. The following morning an increased pulse rate and a rise of temperature, with marked dyspnea, were noted. The next morning a second bronchoscopy was performed, with aspiration of 12 cc of mucus. Twelve hours after this the roentgen picture was practically normal. Thirty-six hours after the second bronchoscopy a third bronchoscopy was performed, and 6 cc of "dirty mucoid material" was aspirated from the right main bronchus.

The second case occurred in a man, 43 years old, who at the time of a fracture of the right leg was suffering from a "cold" and bronchitis. His bronchitis continued and four weeks after the fracture his temperature rose to 103.2 F, his pulse rate to 130 and his respiration rate to 30. The x-ray picture showed "pneumonia" of the left lower lobe. Bronchoscopy was performed. Three centimeters below the carina, in the left main bronchus, a gelatinous secretion too thick to aspirate was sponged up, after which 1 ounce (29.5 cc) of "thick mucopurulent dirty material" was aspirated from the left bronchus. This material contained many pneumococci and streptococci. Immediate relief followed, with the temperature, pulse and respiration normal by the following morning. Sixteen hours after bronchoscopy the lung was almost entirely clear.

A L Brown recently reported bronchoscopic observations in post-operative atelectasis and following therapeutic hyperventilation with carbon dioxide. He concluded that introduction of the bronchoscope may by itself free otherwise firmly fixed bronchial plugs. He noticed the almost complete obstruction of a main bronchus by edema of the mucosa. The effects of carbon dioxide ventilation as seen bronchoscopically were (a) an increased rate and depth of respiration, (b) violent movements of the tracheobronchial tree and alterations in the shape of the lumens of the bronchi, thereby tending to free adherent mucus and (c) a distinct blanching of the mucous membrane of the trachea and bronchi.

Shortly after our report in 1928 of the experimental production of atelectasis, Lee Ravdin, Tucker and Pendergrass reported its experimental production in the dog by the instillation into a bronchus of mucus aspirated bronchoscopically from a patient with postoperative

atelectasis The animal was previously heavily morphinized and subjected to abdominal incision and tight bandaging of the upper part of the abdomen in order to simulate postoperative conditions In the same year we demonstrated the experimental and clinical similarities and relations of postoperative atelectasis, postoperative pneumonia and lobar pneumonia, lobar pneumonia was considered as a "pneumococcic atelectasis"—that is, an accident occurring in the course of pneumococcic bronchitis and occasioned by complete lobar bronchial obstruction by mucus or exudate infected with virulent pneumococci Postoperative atelectasis and postoperative pneumonia were considered as arising in the same manner, but with an occluding exudate infected with less virulent pneumococci The correctness of this hypothesis was supported by the bronchoscopic observations which one of us (Coryllos) carried out in nine cases of lobar pneumonia in which the bronchus to the affected lobes in each case was invariably found occluded with viscid exudate, which was aspirated In a subsequent paper (1930) Coryllos developed this concept in relation to postoperative pulmonary complications

In 1918 Allen O Whipple demonstrated the presence of pneumococci of low virulence in the sputum of patients with or without preoperative bronchitis If postoperative pneumonia developed, the same organism was obtained He expressed the belief that this type of postoperative pneumonia is identical with the mild medical type of lobar pneumonia called "*maladie de Woillez*" (1848), described by Carrière, in which the affected lobe is airless and beefy to feel, and its alveoli are filled with reddish fluid exudate These are indeed the characteristics of the lung in postoperative atelectasis, mild postoperative pneumonia and early red hepatization in lobar pneumonia

The importance of a previous "cold" and bronchitis as factors conducive to postoperative atelectasis, postoperative pneumonia and lobar pneumonia is well known This is explicable in the light of the work of Dochez, Shibley, Mills and Kneeland, who demonstrated the tremendous increase of pneumococci in the throats of monkeys after they had been given a common infectious cold Healthy monkeys seldom showed pneumococci in their mouths and then only in small numbers The part played by a "cold" in preparing the "soil" for growth of pneumococci thus seems apparent In the sputum of acute bronchitis, postoperative atelectasis, postoperative pneumonia and lobar pneumonia, pneumococci are invariably found, and these organisms are the particular ones associated with the production of an exudate viscid enough to cause obstruction of a lobar bronchus Ninety-five per cent of cases of lobar pneumonia are associated with pneumococci, the other 5 per cent being associated with Friedlander's bacillus, which is also outstanding for the viscid type of exudate that it produces Wadsworth showed that gener-



ally the more virulent the microbe, the more fibrinous the exudate is, and this could explain the variable duration of the bronchial obstruction and the toxicity of lobar pneumonia, depending on the virulence of the pneumococcus concerned.

Viewed from this angle, the pathogenesis of postoperative atelectasis (lobar or lobular) and postoperative pneumonia (lobar or lobular) becomes clear, and their close relation becomes evident. Furthermore, these considerations give one a clue to the mechanism of the production of the medical forms of the same diseases—that is, without operation—designated by the names lobar pneumonia and bronchopneumonia, and explain in a simple and clear way a number of peculiarities of these diseases which have so far seemed inexplicable. Take, for example, the case of atelectasis with a considerable volume of mucoid sputum in the trachea and along the walls of the right or left main bronchus, and even into the mouth of the bronchus to the affected lobe. This set of conditions is sufficient under the circumstances to produce atelectasis in a case in which breathing is painful, in which narcosis, morphine or feebleness of the patient has eliminated or reduced the effectiveness of the cough reflex, and in which the patient's position on the "bad" side favors mucus stagnation. Improvement and beginning re-aeration of the lung may occur by spontaneous recovery of an effective cough, or by turning the patient on his "good" side—when a type of internal drainage of the mucus with overflow into the other main bronchus can occur, with a sudden cyanosis and strong spell of coughing, which may bring up large masses or lumps of mucoid material. Often this greatly relieves or cures the patient's dyspnea and cyanosis, and the subjective symptoms leave (L. Sante). As early as 1890 Pasteur tried this treatment combined with artificial respiration. Immediately after such a spell, the lobe will have started re-aeration, a fact easily proved by roentgenograms. When this occurs within a few hours to a day, it would indicate an obstruction relatively limited to a large bronchus. At any rate, complete removal of mucus or exudate along the length of a bronchial airway is not a *sine qua non* for re-aeration of the corresponding lung tissue—it is only necessary that on inspiration air be drawn into the airways by passing between the obstructing mass and the bronchial wall and by this means gradually getting below smaller or larger columns of mucus in a bronchus. The greater the re-aeration, the more effective does cough become. For patchy atelectasis the same mechanism must obtain, the disseminated obstructed lobules becoming gradually but not simultaneously aerated, so that the signs of therapeutic or spontaneous relief are more gradual and not so dramatic as in the lobar type of the disease.

If postoperative pain splinting of the abdomen and chest, lying on the affected side, morphinization and inhibition of the cough reflex

should continue, the stage is set against re-aeration of a lobe or lung. Pneumococci already harbored in the bronchial secretions travel downward into the lymphatics and the finer bronchioles and alveoli with the inevitable outpouring of serum, fibrin and leukocytes. If the virulence of the microbes is moderately high, a more or less toxic state of the patient ensues, and the diagnosis between atelectasis and pneumonia becomes more difficult.<sup>1</sup> Re-aeration of the lung is more difficult, owing to the rapid, shallow breathing, the feebleness of the patient and the occlusion of the finer bronchioles and filling of the alveoli with a variable fibrinous exudate. Should one be dealing with a pneumococcus of high virulence, this mechanism needs only to be extended a step further to give the complete clinical and pathologic picture of lobar pneumonia.

We have described the *contributory factors* which in postoperative atelectasis and postoperative pneumonia are conducive to bronchial occlusion by even a relatively thin exudate—pain, posture, splinting of the abdomen and chest, and inhibition of cough by the anesthetic, narcotics or voluntary effort. This is illustrated by the cases of “drowned lung,” such as the one mentioned, in which Harrington performed seventeen bronchoscopic aspirations of large volumes of thin serous fluid. In the cases in which no operation is performed—that is, in which medical lobar pneumonia ensues—these contributory factors will usually not have been in play. The possibility of physiologic damage to the cilia of the bronchial epithelium or of a decreased sensibility of the mucosal cough reflex which follows a preceding bronchitis must be admitted. Nevertheless, cough—the “watch-dog” of the lung—and bronchitis have usually been present. In spite of the preceding cough, a dramatic onset with chills and fever ushers in the acute catastrophe—a pneumococcic bronchial obstruction which is an accident in the course of a pneumococcic bronchitis. When this happens, we are apt to forget or to overlook the fact that the “makings” of the drama have previously been at hand, and we say that there have been no premonitory symptoms. Aside from preliminary bronchitis, the patient has been well. The inquiring mind will ask how it is that lobar pneumonia is not more

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1 It is too early as yet to judge the therapeutic value of artificial pneumothorax, which Coghlan recently applied in six cases of lobar pneumonia. Marked clinical relief and therapeutic value are claimed by this author using this procedure. Similar clinical relief and therapeutic value have been reported for pneumothorax in postoperative atelectasis by Farris, Elkin and Habliston. Without discussing here the theoretical merits or the objections to pneumothorax, we wish to point out that the symptomatic relief reported as obtained by its use appears to be further evidence of the close relationship existing between postoperative atelectasis and lobar pneumonia (lobar pneumococcic atelectasis). In both conditions pneumococci are present in the sputum, and we consider these diseases as different phases in the same syndrome—pneumococcic bronchial obstruction.

frequent, if lobar bronchial occlusion is its immediate cause, considering the wide prevalence of bronchitis with sputum infected with virulent pneumococci. For it is known that the proportion of cases of lobar pneumonia to cases of acute bronchitis is less than the proportion of cases of postoperative atelectasis and postoperative pneumonia to cases occurring after abdominal or thoracic operations. The answer is that postoperative cases may have any or all of the contributory factors mentioned working to favor the production of pneumococcic atelectasis. In lobar pneumonia these factors have not been at hand, and this is why the incidence of pneumonia in acute bronchitis is relatively small. For this reason, when lobar pneumonia occurs spontaneously or following acute bronchitis, some unusual factors have been at play to cause bronchial obstruction, and these to our mind are the high virulence of the organism, the extreme (fibrinous) viscosity of the exudate which was initially able to occlude a lobar bronchus, and the allergic edema of the bronchial mucosa. Consequently, when "lobar pneumonia" ensues, the toxicity of the patient exceeds that of the patient with postoperative atelectasis or pneumonia. To the objection that there are no premonitory signs or preliminary bronchitis in lobar pneumonia the answer may be given that in postoperative atelectasis or postoperative pneumonia, also, there are no premonitory signs or symptoms, the disease starts within from twelve to twenty-four hours after a sterile operation whether done under local, spinal or general anesthesia. In other words there need not be an apparent preliminary cold or bronchitis, but it cannot be denied that postoperative pulmonary complications as well as medical lobar pneumonia occur relatively more frequently when a preliminary cold or bronchitis has existed. Austrian went so far as to say that if in lobar pneumonia a preliminary bronchitis has not been found it is because this condition has not been looked for. The facility with which, in a common cold, the nasal mucosa becomes so edematous as to obstruct breathing completely suggests at once that inflammatory or allergic edema of the bronchial mucosa can be an important contributory factor in complete obstruction of a lobar bronchus in pneumonia. Brown noted marked bronchial edema in atelectasis. In lobar pneumonia, after the initial bronchial occlusion with exudate, a pneumococcic invasion of the parenchyma occurs concomitant with the absorption of air and development of atelectasis. With the fibrinization and coagulation of the exudate, the infection may be considered as "fixed" below an obstruction, in an environment with little or no oxygen. We have previously shown (1929 [6]), that growth of pneumococci is markedly enhanced by moderately decreased oxygen tension in the medium. The experimental groundwork for this concept will be presented under "Experimental Data" and elaborated under "Comment." Groups 6 and 7 are of unusual interest in that they constitute the first reported

instances of experimental production of lobar pneumonia with human pneumonic sputum

## EXPERIMENTAL DATA

The experiments were carried out on dogs weighing from 10 to 12 Kg. Before bronchial manipulation of whatever nature the animal was anesthetized with sodium amytal (sodium iso-amyl-ethyl-barbiturate) 55 mg per kilogram being given intraperitoneally. Reference to table 1 will show the seven types of experiments that were done.

TABLE 1—*Experimental Data*

Experiment	Agent	Procedure	Pathologic Condition Produced	Clinical Toxicity	Outcome	Reference to Figures in Text
1	Sterile balloon	Lobar bronchus obstructed 16-24 hr with balloon	Atelectasis	Little or none	Recovery, re-aeration of lung	1
2	Sterile balloon	Lobar bronchus obstructed more than 24 hr with balloon	Atelectasis plus serous exudate plus acute exudative lobar pneumonia, if prolonged, necrosis in lung and purulent pleurisy, histologically, extreme diffuse exudation of pus cells with areas of necrosis	Mild to severe, depending on duration of obstruction	Recovery if removed within a few days, fatal if prolonged	1
3	Pneumococcus culture of low or moderate virulence	2 cc of broth containing the sediment from a centrifuged amount of 18 hr broth culture (1 cc per Kg of the dog's body weight) sprayed into right or left main bronchus	No bronchitis or mild bronchitis or pneumonia with haziness over affected area in roentgenogram, with moderate variable shift of mediastinum and heart, and elevation of diaphragm in other cases pneumonia (lobar pneumonia) with classic roentgen signs—monolobar types of disease frequent, nonresolution and pleurisy possible	None to moderate	Usually recovery if no complications arose, with gradual return of heart and mediastinum to normal position and re-aeration of lung	2 (A, B, C and D) 3 (A, B and C) 4, 5 and 6
4	Pneumococcus culture of high virulence	Same as in experiment 3	Acute pneumococcal atelectasis (lobar pneumonia), slight serous pleural effusion containing pneumococci, positive blood culture, histologic appearances of lung identical with those in human pneumonia	High	Usually fatal	7 and 8
5	Pneumococcus culture of moderate virulence plus obstructing balloon	Tip of balloon dipped in concentrated culture and then used in obstruction of lobar bronchus	Same as in experiment 4	High	Usually fatal	9
6	Human pneumonic sputum containing pneumococci of low or moderate virulence	5-6 cc instilled into right main bronchus	None or mild bronchitis or pneumonia or pneumococcal atelectasis	None to moderate	Recovery	10 and 11 (A, B, C and D)
7	Human sputum containing pneumococci of high virulence	5-6 cc instilled into right main bronchus	Acute pneumococcal atelectasis (lobar pneumonia) with slight pleural effusion (serous), histologic appearance of lung identical with those in human pneumonia	High	Fatal	12 and 13

(Three hundred and ten dogs were used for the experiments of groups 1, 2, 3, 4 and 5, already described in previous publications )

GROUP 1—Our sterile obstructing balloon was placed in the left or right bronchus, inflated and left in for from sixteen to twenty-four hours. During this period atelectasis ensued with slight fever, an increased rate of respiration, cough and typical roentgenographic signs. On removal of the balloon, gradual re-aeration in from sixteen to

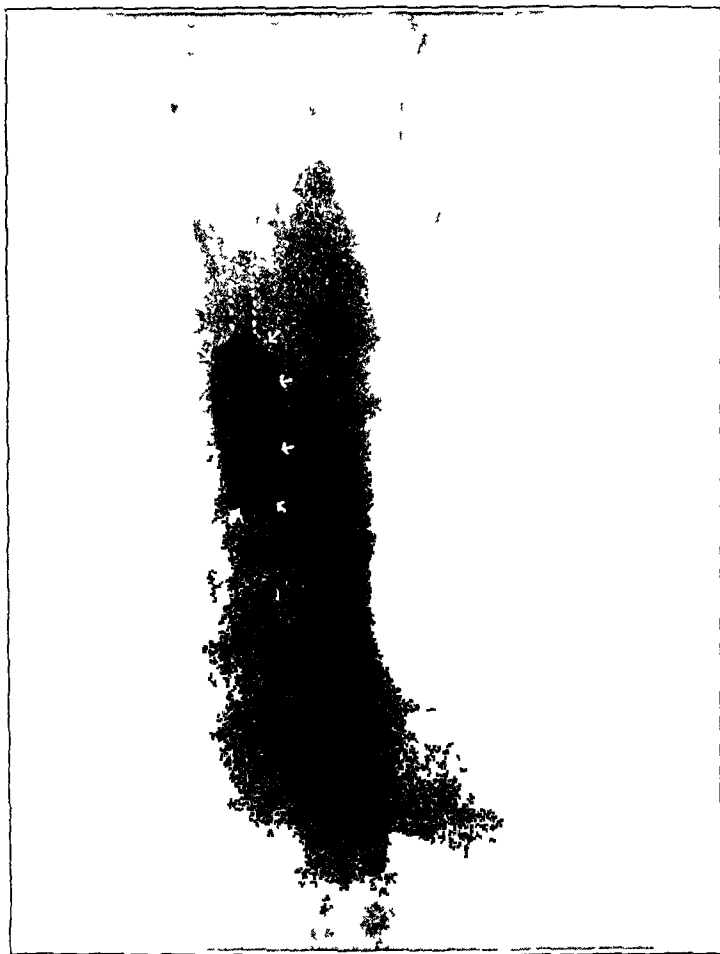


Fig 1 (dog 47) —A roentgenogram taken twenty-four hours after obstruction of the right main bronchus with a special balloon, complete right massive atelectasis is seen. If obstruction is prolonged for from three to ten days, acute exudative pneumonitis, pulmonary necrosis, abscess, purulent pleurisy and death may ensue.

twenty-four hours was noted by roentgenogram, accompanied by considerable "dry coughing." There was little or no clinical toxicity (fig 1).

GROUP 2—The "obstructing balloon" was left in over twenty-four hours. The pathologic changes produced depended on the duration of obstruction and varied from a serous alveolar exudate to one with more

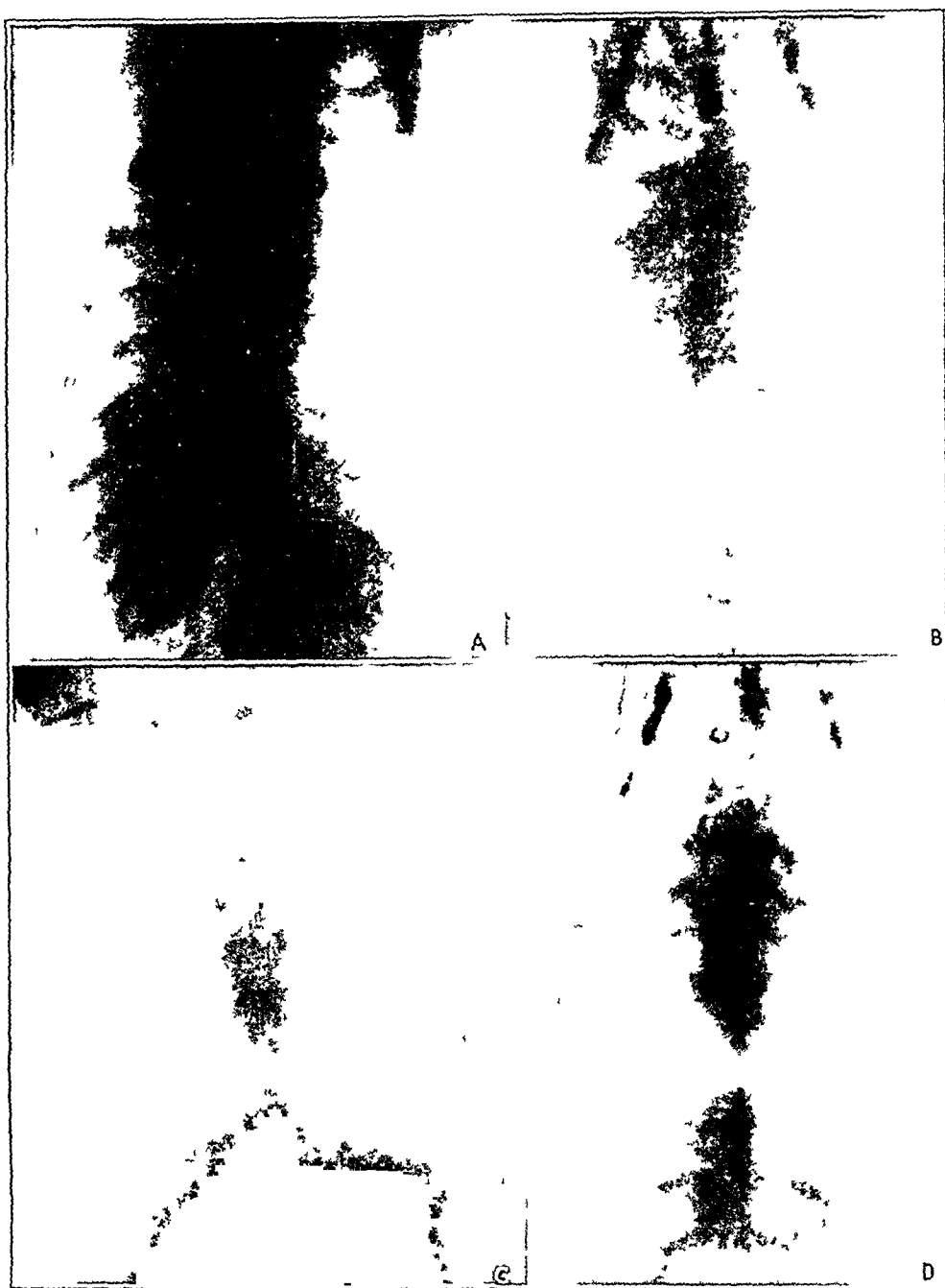


Fig 2 (dog C45) —The spontaneous cure of lobar pneumonia (pneumococcic atelectasis) is illustrated. *A* shows the lung twenty-four hours after insufflation of 6 cc of an 18 hour old broth culture of *Pneumococcus*, type I, into the right main bronchus, complete lobar pneumonia (pneumococcic atelectasis) has occurred. *B*, taken seventy-two hours after insufflation of culture, shows that the heart is on its way back to the left. The right lower lobe is clear, the right middle and upper lobes are still hazy. *C*, taken ninety-six hours after inoculation, shows the lung almost clear. *D*, taken five days later, shows the lungs clear and the heart back on the left.

or less exudation of polymorphonuclear cells into the alveoli and bronchiolar obstruction with this exudate. At a later stage acute, purulent pneumonitis was produced, with extensive exudation of polymorphonuclear cells into the alveoli and areas of pulmonary necrosis. At this stage there was also diffuse, purulent pleurisy. Grossly, the lungs were diffusely gray and consolidated and sank in water. Cut sections exuded

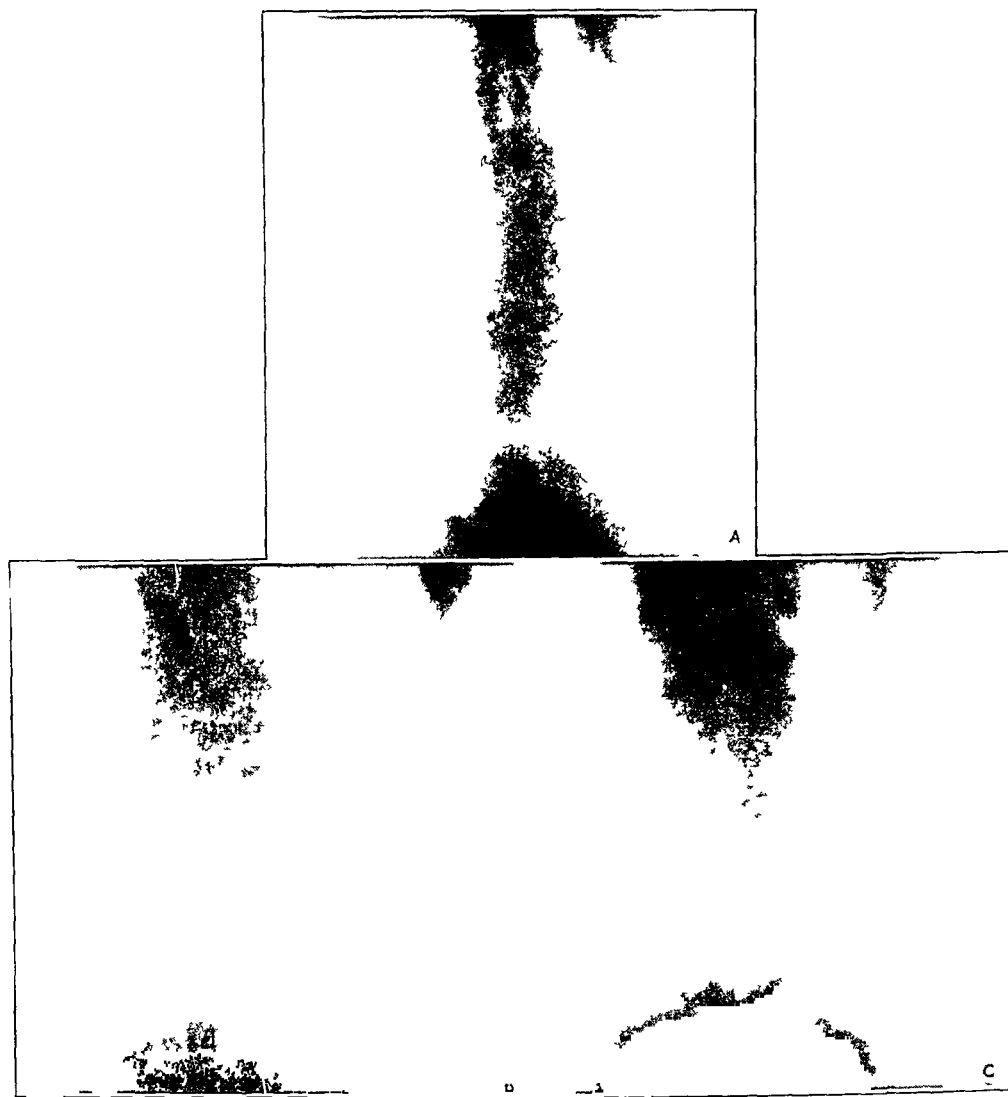


Fig 3 (dog 741) —The figure illustrates an “unresolved” pneumonia of the right upper lobe resulting in pulmonary necrosis and abscess. *A* is the control film before insufflation of pneumococcus culture into the lung. *B*, taken three days after insufflation of 2 cc (the concentrate of 14 cc) of pneumococcus culture into the right main bronchus, shows the right lower lobe hazy and the right upper lobe definitely involved. *C*, taken thirteen days after insufflation, shows the right upper lobe still involved (“unresolved pneumonia”). The animal died on this day.

a dirty gray, purulent material from the bronchioles and alveoli. The animals generally succumbed to such obstruction if it was continued

for more than from three to ten days, with severe general toxic symptoms. On the other hand, removal of the obstructing balloon before this length of time as a rule resulted in recovery.

GROUP 3—From 1 to 1.5 cc of a culture of *Pneumococcus*, type I, of low or moderate virulence was given per kilogram of weight. This culture was a broth culture prepared from a pneumococcus not recently "passed" through the peritoneum of a mouse to augment its virulence. The calculated volume of culture, from 18 to 20 hours old, was centrifuged, the sediment suspended in from 1.5 to 2 cc of broth and sprayed into the right or left main bronchus of the dog by means of a bronchoscope. Generally little or no toxicity was evidenced with moderate rise



Fig. 4 (dog 741) — *A* is the abscess in the "unresolved" pneumonic right upper lobe, *P-P'* are areas where this lobe was adherent to the parietal pleura. The entire right upper lobe was markedly shrunken and liver-like. (The right upper lobe is indicated by arrows.)

of temperature and leukocytosis and little or moderate cough. The roentgenograms twenty-four hours after insufflation of the culture were negative or showed slight or moderate haziness over the affected lobes. In most instances, a moderate variable displacement of the heart and mediastinum to, and elevation of the diaphragm on, the affected side were noted. In a small proportion of cases a typical picture of atelectasis of low or moderate clinical toxicity was produced. In this group we obtained a greater proportion of monolobar involvement. Complete recovery was the rule, but in a few instances "nonresolution" with



a typical pathologic picture of lobar pneumonia was produced (figs 2 *A*, *B*, *C* and *D*, 3 *A*, *B* and *C*, 4, 5 and 6)

GROUP 4—A culture of a highly virulent pneumococcus was used, the broth culture being prepared from a strain just "passed" through a mouse. Practically a single pneumococcus, when intraperitoneally injected, was sufficient to kill a mouse. An amount of an 18 to 20 hour old culture equivalent to from 1 to 15 cc per kilogram of weight was centrifugated and the sediment was suspended in from 15 to 2 cc of broth and insufflated into the right or left main bronchus of the dog. Within from eighteen to twenty-four hours the animals



Fig 5 (dog 741) —A low power photomicrograph through the abscess of the right upper lobe

were very toxic or moribund, with marked leukopenia and a relative excess of polymorphonuclears (from 500 to 2000 white blood cells, from 95 to 98 per cent polymorphonuclears), also subnormal temperature, dyspnea and rapid, shallow breathing. Blood cultures were positive in the majority of cases. The roentgenograms showed a classic atelectasis, i. e., a marked deviation of the heart and mediastinum to, and an elevation of the diaphragm on the affected side. At postmortem examination, the affected lobes were indistinguishable by appearance alone from the atelectatic lobes in simple bronchial obstruction of twenty-four hours' duration. The lobar bronchi were

practically always occluded with a dirty, serosanguineous fluid which was more or less frothy and moderately thin. They sank in water, were uniformly deeply bluish red, and were smaller than the normal lobes when the trachea was clamped previous to opening the chest, and a little more edematous to touch than the atelectatic lobes in simple bronchial obstruction. In animals dying within from twenty-four to

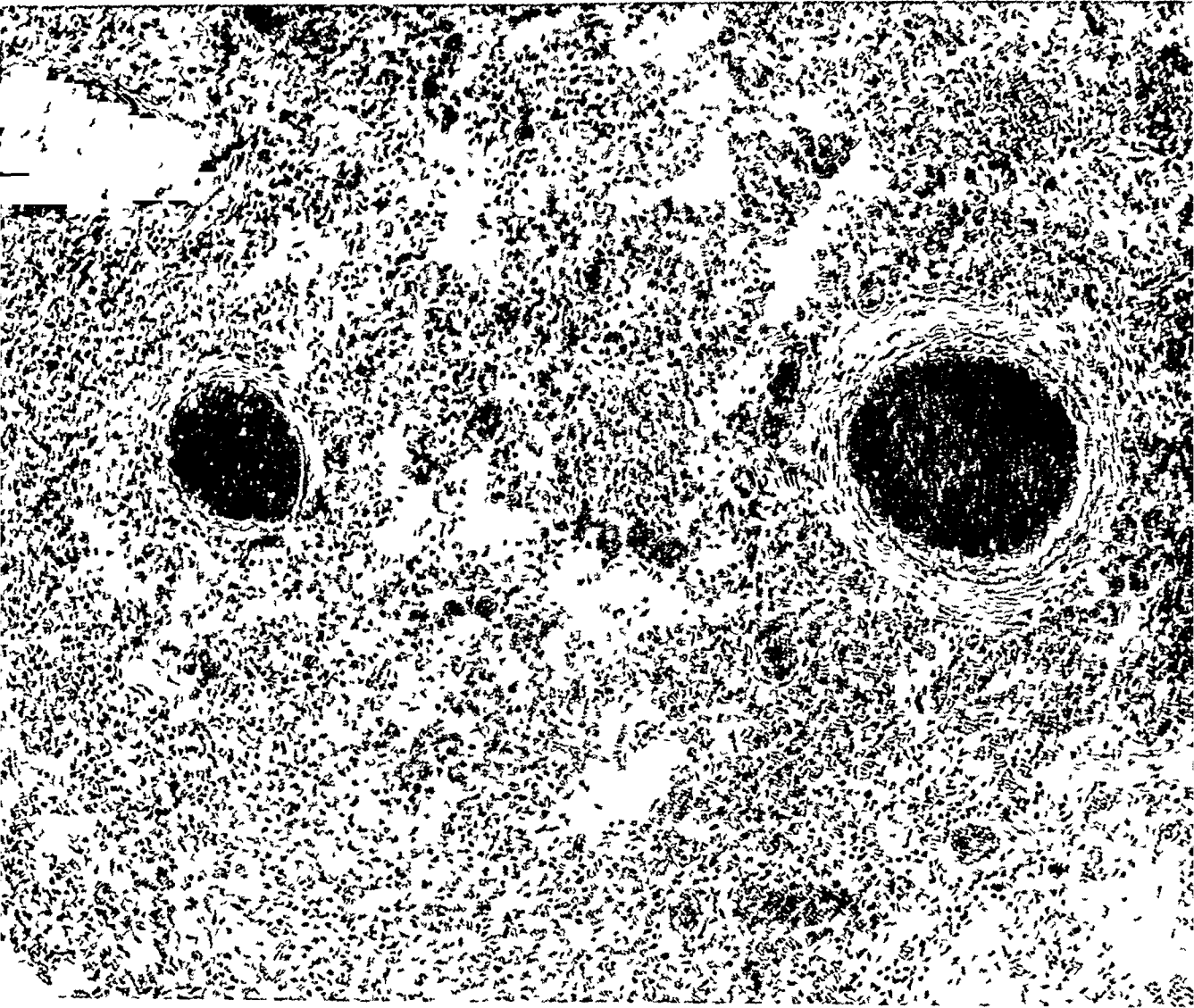


Fig 6 (dog 741) —A high-power photomicrograph of the “unresolved” right upper lobe. This section is characteristic of the rest of the lobe. Note the dilated precapillary arterioles and the exudation of serum and leukocytes into the alveoli.

thirty-six hours after injection, the affected lobes were rather friable cut sections exuding a moderately thick, dirty gray, serosanguineous material from the bronchioles. Animals dying after three days showed the diffusely irregular pinkish-gray mottling of early gray hepatization, when the bronchiolar and alveolar exudates were more

frankly gray and purulent. Microscopically, the picture shown in the sections was practically identical with that of human lobar pneumonia (sections examined by Dr. Douglas Symmers). Generally, however, the animals succumbed within forty-eight hours, with the lungs in the stage of "red hepatization" and with a slight serous pleural effusion containing pneumococci (figs 7 and 8).

GROUP 5—The end of the obstructing balloon was merely dipped in a culture of a pneumococcus of moderate virulence (concentrated by the

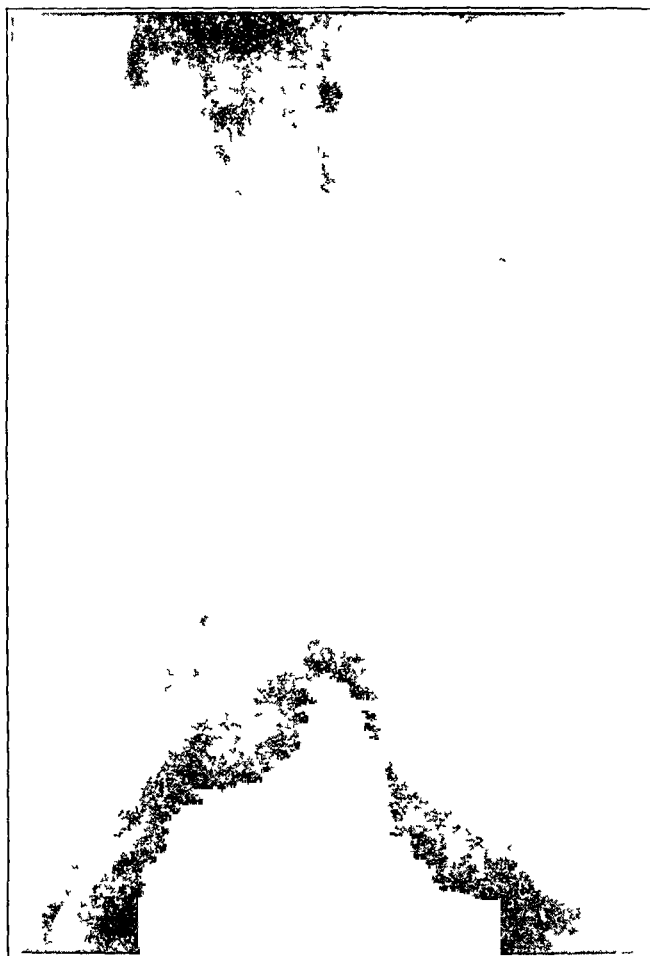


Fig 7 (dog 734)—Twenty-four hours after insufflation of 11 cc of pneumococcus culture (concentrated to 15 cc) into the right main bronchus, a complete right lobar pneumonia (pneumococcic atelectasis) has occurred. This pneumonia was fatal in four days.

technic used for groups 3 and 4) and the balloon was introduced into the right or left bronchus of a dog (by the technic used for groups 1 and 2) and inflated to obstruct the bronchus completely for from eighteen to twenty-four hours. (Six dogs were used in this group.) Whether the balloon was removed or not the animals succumbed

generally within from twenty-four to forty-eight hours after its introduction, and the findings and results were similar to those in group 4 (*q v*). In other words, a culture of moderate virulence was by this method able to produce a clinically high toxic picture (heart's blood and pleural exudate positive for pneumococci) and marked pathologic results. The infection appeared to have been "fixed" in the lung by

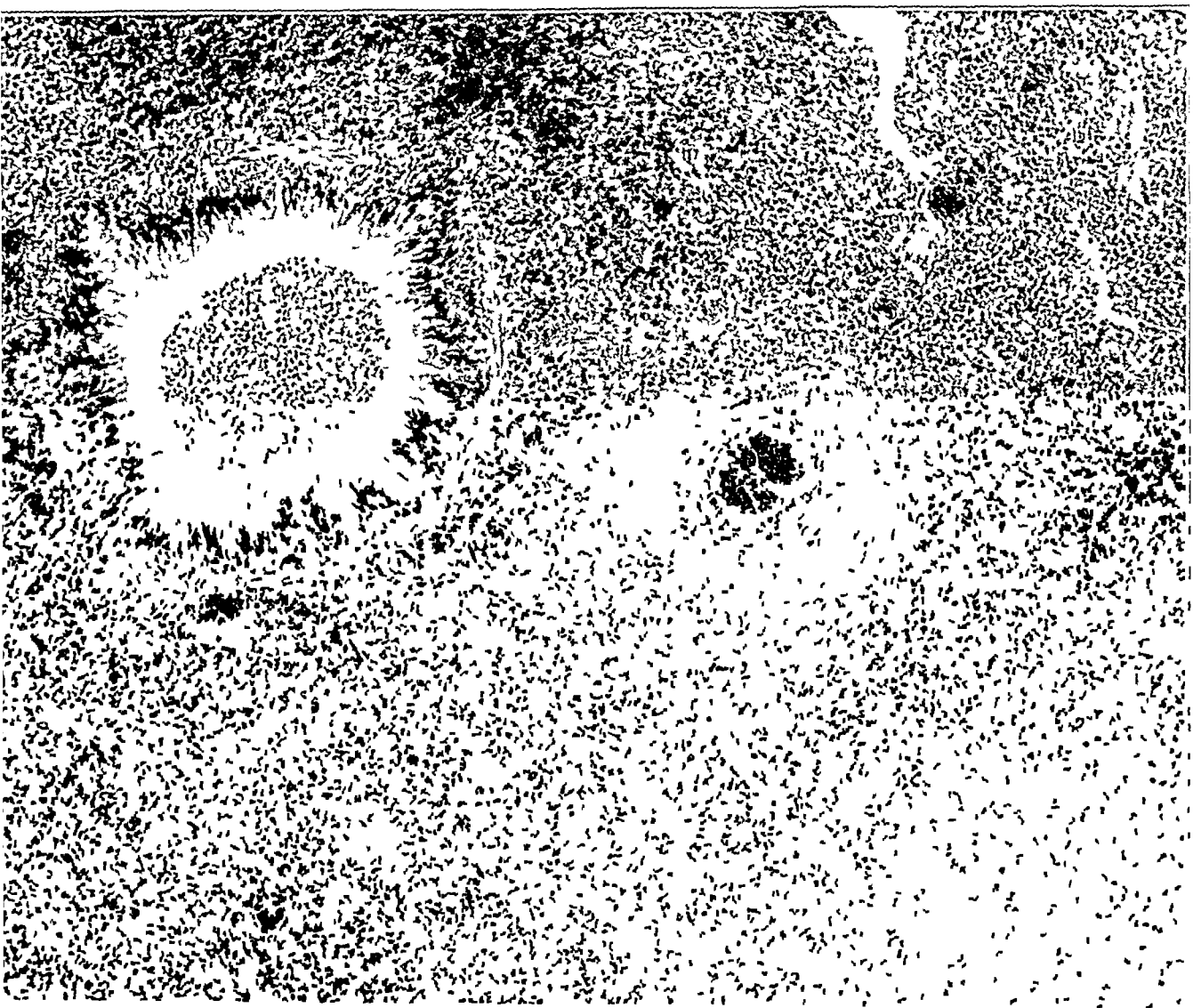


Fig 8 (dog 734) —A high power photomicrograph of the right upper lobe

the obstruction balloon, so that removal of the latter did not influence the fatal outcome. While the air was being absorbed, the infection traveled deep into the lymphatics and parenchyma and gave toxicity comparable to that of group 4. Another factor must be considered to account for the severity of symptoms and signs, namely, the enhancement of growth of pneumococci, which we have previously shown occurs *in vitro* with cultivation under reduced oxygen tension. Judged by

clinical symptoms, the virulence of the infection was raised by mechanical obstruction above the infection (fig 9)

GROUP 6—To our knowledge we are the first to have experimentally produced atelectasis or lobar pneumonia with human pneumonic sputum (dogs 639 and 640, weight, 8 Kg)

Here fresh sputum from pneumonic patients with little evidence of toxicity was used. Six cubic centimeters of sputum freshly obtained was



Fig 9 (dog 38)—Twenty-four hours after obstruction of the right main bronchus with our special balloon, which was first dipped into an 18 hour old (ten times concentrated) culture of pneumococcus, the right lower and middle lobes were involved. This animal died with a rapidly fatal pneumococcic atelectasis (lobar pneumonia) and bacteremia.

instilled through the bronchoscope into the right or left main bronchus of each dog (previously anesthetized). After twenty-four hours or more, few or no clinical symptoms or toxicity had been produced. A mild cough, bronchitis or a slight haziness in the roentgen ray pictures with moderately variable degrees of deviation of the heart and mediastinum to, and elevation of the diaphragm on, the affected side were

noted In one group, in which sputum of viscosity 90 was used, only a cough and moderate elevation of temperature were produced, with no other characteristic signs (dogs 649 to 650) Occasionally a typical atelectasis was produced (figs 10 and 11 *A, B, C* and *D*), which resolved and gradually returned to a normal roentgen aspect This type of atelectasis is directly comparable with that produced experimentally by Lee, Ravdin, Tucker and Pendergrass, using sputum from a patient with postoperative atelectasis, which they instilled into the bronchus of

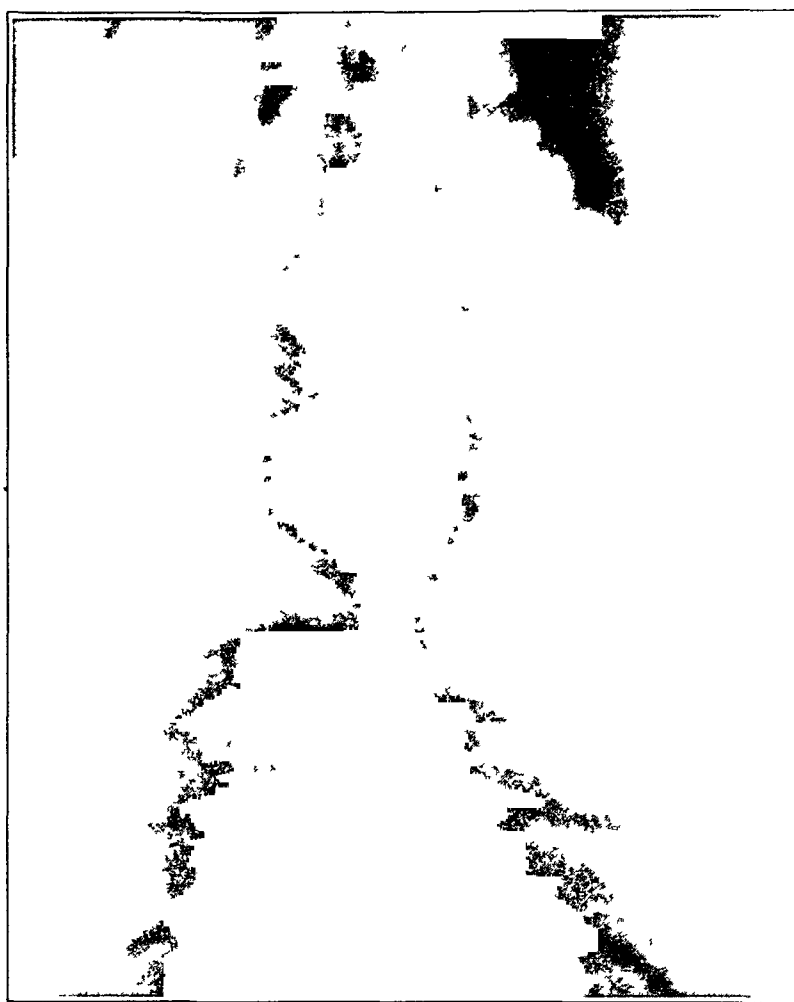


Fig 10 (dog 639) —A roentgenogram illustrating the experimental production of lobar pneumonia (pneumococcic atelectasis) with human pneumonic sputum, with spontaneous recovery This x-ray picture was taken twenty-four hours after the instillation into the right lower bronchus of 6 cc of sputum from a patient suffering from lobar pneumonia whose blood culture was negative The right lower lobe is hazy, and the right diaphragm, elevated

a dog that had been submitted to morphine narcosis, laparotomy and tightly constricting abdominal bandaging It will be recalled that all postoperative atelectatic sputums contain pneumococci, including the sputum which these authors used The history of the patient whose sputum was used in group 6 follows

J O , aged 29, a white man, was admitted on Feb 9, 1931, to Bellevue Hospital, in the service of Dr Eugene F DuBois. He had had a cough since February 2, which became productive with rusty sputum on February 7. On February 8, the day before admission, he had had chills, fever and pain in the right side of the chest and had vomited. On admission on February 9, physical examination showed involvement of the right upper lobe alone. His temperature was 101 F, pulse rate, 110, respirations, 26. The white blood cell count was 16,400, with 92 per cent

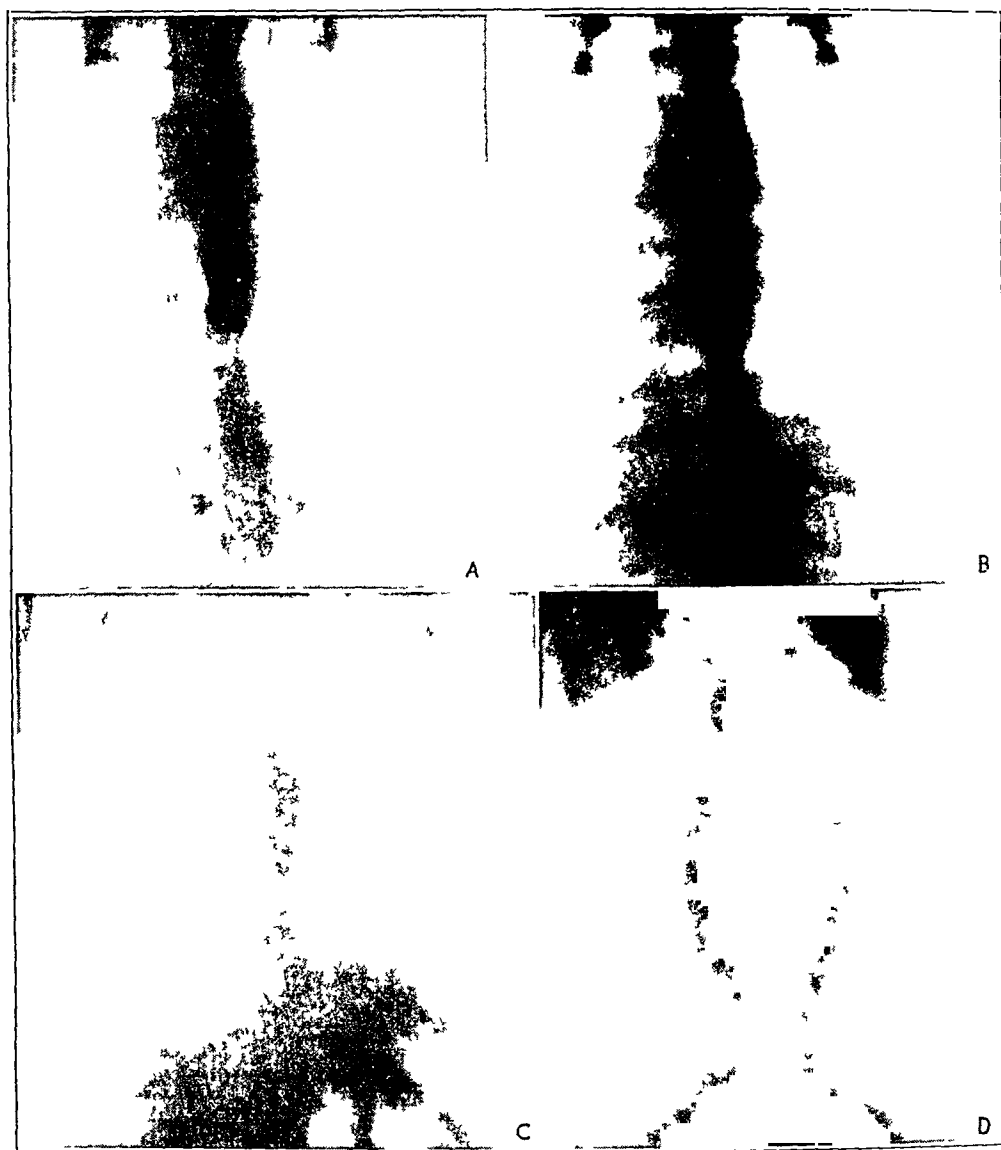


Fig 11 (dog 639) — *A* taken two days after instillation of sputum, shows a very definite involvement of the right lower lobe (lobar pneumococcal atelectasis) with marked dextrocardia. *B*, taken three days after instillation of human pneumonic sputum into the right main bronchus, shows a slight clearing of the lower lobe and partial return of the heart to the left. *C*, taken five days after instillation of sputum, shows the lung practically normal and the heart almost entirely back in its normal position. *D*, taken six days after instillation of sputum, shows the lung normal and the heart in normal position.

polymorphonuclears. A blood culture was negative. On February 10, his temperature rose to 103 F, the pulse rate was 120, the respirations, 24, with profuse coughing up of rusty sputum containing pneumococci of group I. The next day the temperature declined sharply to 100 F (pulse rate, 100, respirations, 20), and his cough was slight and hardly productive. The temperature never rose above 100 F from this point on and gradually declined to normal. He was discharged on Feb 24, 1931.

Sputum for the experiment was obtained on Feb 10, 1931, two days after the onset of the disease. Its viscosity was 10.



Fig 12 (dog 627) —Twenty-four hours after instillation of 10 cc of sputum from a pneumonic patient with a positive blood culture, this animal succumbed to complete right lobar pneumonia (pneumococcic atelectasis). The x-ray picture was taken after death.

GROUP 7—In this group (dogs 627 and 628, weight, 12 Kg) 10 cc of freshly obtained sputum from a highly toxic patient with a positive blood culture was instilled through the bronchoscope into the right main bronchus of each dog (previously anesthetized). The animals were moribund within twenty-four hours, with the classic roentgen signs of pneumococcic atelectasis, and died within forty-eight hours.



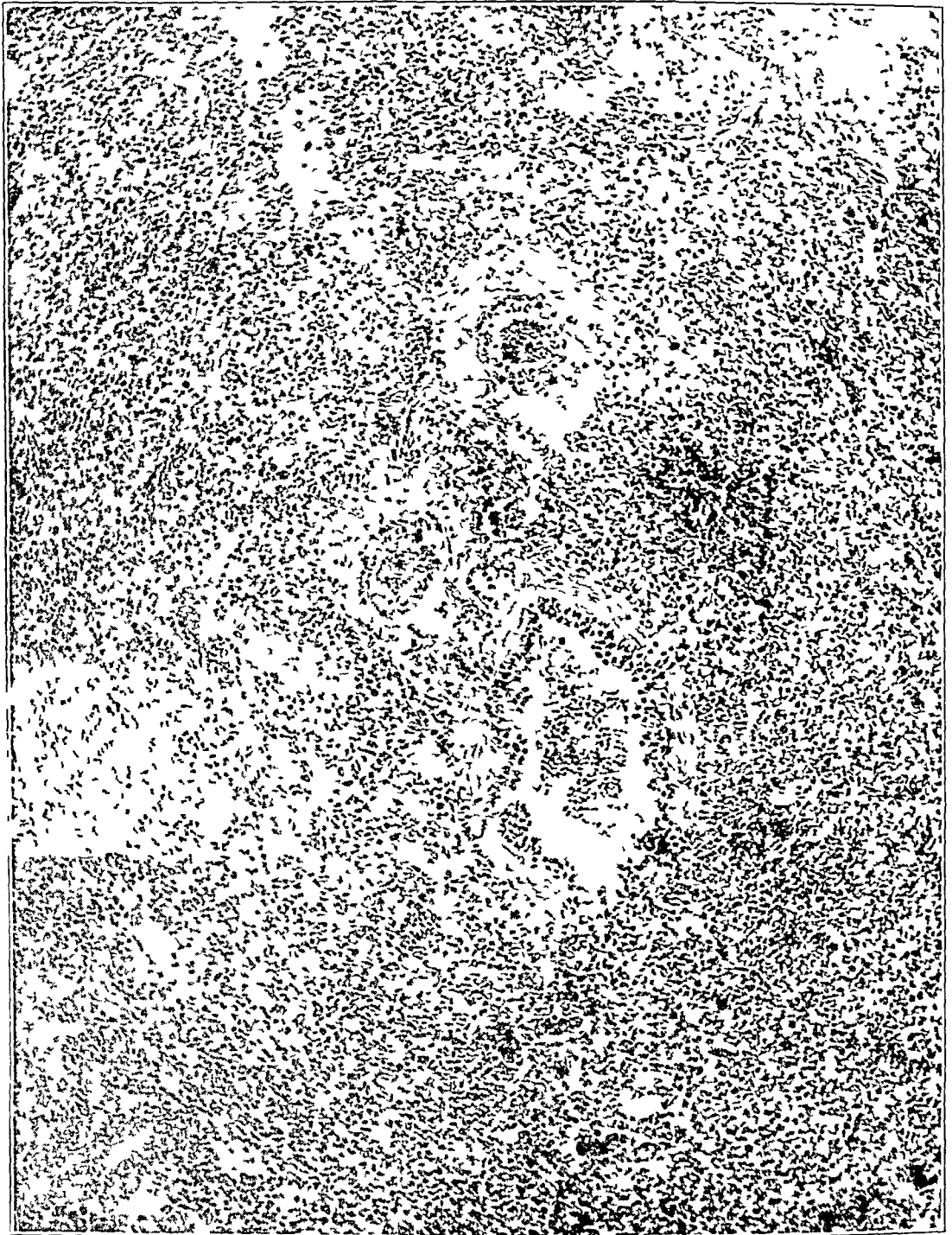


Fig 13 (dog 627) —A photomicrograph of the pneumonic lung

The lungs were in the state of red hepatization, deeply reddish blue, and indistinguishable in appearance from atelectatic lungs. Grossly and microscopically, they had all the characteristics of the lungs of group 4 and of human pneumonic lungs in the stage of red hepatization. The pleural cavity contained a small amount of serous fluid (figs 12 and 13). The history of the patient whose sputum was used for this group follows.



Fig 14—Photograph of a human pneumonic lung showing complete bronchial obstruction by a cast (courtesy of Dr Norbert Enzer, Mount Sinai Hospital, Milwaukee). The blood culture was positive for pneumococcus, type I.

F. R., aged 40, a white man, was admitted on Jan 19, 1931, to Bellevue Hospital, in the service of Dr Eugene F. DuBois. He gave a history of a previous cold. Twenty-four hours before admission he had had a chill with pain over the fifth and third ribs on the right side. On admission, his sputum was "bloody." His temperature was 104 F, his pulse rate was 120, his respirations, 26. Physical examination showed involvement of all the lobes on the right side. The white blood cell count was 14,000, with 90 per cent polymorphonuclears. A blood culture taken on January 22 was positive for *Pneumococcus*, group I. The sputum was likewise positive for group I. A blood culture made on January 24 was nega-

tive His temperature ranged between 102 and 103 F from January 20 to 23, when it declined to 100 and rose to 102 on the same day On January 25, his temperature fell to 100 F (pulse rate, 90, respiration rate, 18), gradually declining to normal On February 2, a left sternoclavicular arthritis developed, which spontaneously cleared By February 20, his lungs were clear, and he was discharged on Feb 24, 1931

Sputum for the experiment was obtained on Jan 20, 1931, two days after the onset of the disease Its viscosity was 30, and the  $p_{H}$ , 7.4

#### COMMENT

Reference has been made to the extreme viscosity of the pneumonic sputum The deleterious qualities of pneumonic exudate reside not only in its viscosity, but also in its content of virulent pneumococci and the presence of fibrin, the coagulability of which is a serious drawback to drainage of the finer bronchioles and parenchyma The sputum of atelectasis and that of pneumonia cannot be rigidly classified, for the former also has a content of pneumococci and the change from one to the other could occur by slow degrees with increasing virulence of pneumococcic content At any rate sputum coughed up is not necessarily an index of the type of bronchial mucus or exudate occluding a lobe of the lung Sputum coughed up may represent merely an overflow from the bronchus of the affected lobe It would be difficult for example, to conceive of the hemorrhagic rusty sputum in pneumonia as coming entirely from the parenchyma proper when the lung is filled with coagulated fibrinous exudate, moreover, the actual quantity of sputum coughed up is very small, as compared with the volume of exudate of an affected lobe as seen post mortem Should pneumonic sputum have a high content of mucoid material, its origin from the alveoli proper is precluded, for mucous glands exist only in bronchi of a diameter of 1 mm or more An overflow from the mouth of a lobal bronchus is perfectly compatible with its still remaining perfectly occluded with mucus and exudate and the parenchyma filled with a fibrinous exudate

We have produced "full-blown" and rapidly fatal experimental lobal pneumonia by instillation of 10 cc of only moderately viscid sputum (viscosity 30) obtained on the second day of disease from a toxic pneumonic patient with a positive blood culture, this sputum was instilled into the main bronchus of an anesthetized dog On the other hand, with other sputum of viscosity 90 or more as compared with water obtained from a less toxic patient only evanescent pneumonitis with early symptoms of atelectasis (a moderate shift of the heart and mediastinum and an elevation of the diaphragm) was obtained The ease of experimental production of the signs of atelectasis appears therefore, to be related not only to viscosity but also to the virulence of the pneumococcic content We have shown that 1 cc of a ten times concentrated broth culture of a virulent strain of pneumococci is suffi-

cient to cause pneumococcic atelectasis when sprayed into the bronchus of a dog anesthetized with amytal. The sputum of atelectasis invariably contains pneumococci, and Lee, Ravdin, Tucker and Pendergrass were able to reproduce the signs of atelectasis by instilling "atelectasis sputum" into the bronchus of a dog with the aid of abdominal incision, constricting abdominal bandages and morphinization. Their experimental production of atelectasis is comparable to that in our group 6, in which we produced atoxic atelectasis by human pneumonic sputum containing pneumococci of low or moderate virulence. Furthermore, we believe that the experimental cases in which we produced mildly toxic states, together with typical shift of heart and mediastinum and elevation of the diaphragm, by bronchial injection of a culture of a moderately virulent pneumococcus or by moderately virulent human pneumonic sputum stand in more direct analogy to clinical cases of postoperative atelectasis which, because of the growth of pneumococci in the bronchial secretions or alveolar exudate, border on or merge into a toxic state and are commonly known as cases of "postoperative pneumonia." The only distinction, if any, that clinically can be made between postoperative atelectasis and postoperative pneumonia is the greater toxicity of the patient, for the physical and roentgen signs are identical in both instances. Only too often the clinician cannot be sure whether he is dealing with pneumonia complicating atelectasis or with atelectasis complicating pneumonia.

Standing as an extreme phase in the syndrome of pneumococcic bronchial obstruction and as a condition analogous to severe postoperative pneumonia or medical lobar pneumonia is the experimental lobar pneumonia (pneumococcic atelectasis) which we produced by insufflation of a culture of a highly virulent pneumococcus or by instillation of 10 cc. of human pneumonic sputum from a toxic patient into the bronchi of dogs. These animals were extremely sick or moribund, with roentgen signs of atelectasis, marked toxic leukopenia, polymorphonuclear cytosis, subnormal temperatures and positive blood cultures. In this regard it is noteworthy that elevation of the diaphragm on the diseased side and variable degrees of mediastinal shift to the same side are often noted in human lobar pneumonia. Never in uncomplicated pneumonia is the mediastinum or the heart deviated away from the diseased side, indicating that the pneumonic lobe is never larger than the corresponding healthy one, as we first showed (1929).

It should be remembered that an infection in the lung, as elsewhere, which is toxic for one patient may be less toxic for another, and this consideration further decreases the possibility of arbitrarily marking off the phases of pneumococcic bronchial obstruction by clean-cut dividing lines.

That the phenomenon of pneumococcic atelectasis of a lobe may occur with relatively thin exudate might be accounted for by the dele-

terious effect of the latter on the ciliated epithelium, by the greatly diminished effectiveness of cough in an enfeebled toxic patient, or by both, and by the edema of the bronchial mucosa. The initial period of complete obstruction of a lobar bronchus, whether by thick or by thin exudate or by mucopus, need not be long before a generalized bronchial and alveolar outpouring of serum, polymorphonuclear cells and fibrin occurs, once this takes place, re-aeration of the myriads of alveoli and bronchi becomes very difficult.

The objection has been raised that in lobar pneumonia or even postoperative pneumonia, no "plug" is found in a lobar bronchus. "Plug" should not be taken to mean a corklike type of occlusion at one point in the bronchial tree. It refers to a variable column or mass of fluid or semifluid, mucoid or fibrinous secretion or exudate. It is not expected, therefore, when a bronchus is cut open, to find a more or less firm obstruction. The cutting of the bronchus disrupts and dissipates the obstructing column along the wall of the bronchus. Furthermore, the rapid autolysis of exudate after death accounts for the absence of firm exudate in, and obstructing, a large bronchus, the smaller bronchi remain obstructed. This also accounts for the frothy fluid found in the bronchus post mortem which was not present during life.

It is evident that in postoperative atelectasis re-aeration can and does usually occur coincident with profuse expectoration and cough. Since it is obviously impossible for an airless lung to empty itself of exudate by the compressive phase of cough, this must be accomplished by the gradual ingress of air between the obstructing material and the bronchial wall, so that there is some force below the obstruction to expel an occluding column or mass of exudate. The greater the re-aeration the more effective does cough become, and it is obviously the deep inspiratory phase of deep cough which accomplishes this re-aeration and gradual expulsion of foreign material. This process of "resolution" would seem reasonably to hold for moderate or severe types of lobar pneumonia as well. The lung in which postoperative atelectasis or postoperative pneumonia is present may take from ten to fourteen days or more to "resolve" and re-aerate, and the lung in which an abortive or short-lived pneumonia is present may "resolve" and re-aerate in a few days. On the other hand, the lung in which a postoperative atelectasis or a postoperative pneumonia is present can "resolve" and re-aerate within a few days, and the lobe in which a lobar pneumonia is active may take from ten to fourteen days or more to "resolve" and re-aerate. In both instances—postoperative atelectasis or pneumonia and lobar pneumonia—the marked clinical relief sets in long before the roentgen and clinical aspects of the disease indicate complete re-aeration and long before the coughing up of mucopus or exudate has ceased.

In all three conditions the amount of edema in the lung or of fibrin in the exudate may be an important factor in determining the rapidity of "resolution," drainage and re-aeration. In those types of lobar pneumonia with considerable fibrinous exudate, it is likely that liquefaction is greatly aided by the two proteolytic enzymes (Opie and Lord, Jobling and Strouse, Ascoli and Bezzola, Bittoif) liberated by the white cells in the exudate, after the exudation into the lung of anti-tryptic substances in the serum has ceased. One of the enzymes is effective in neutral medium and the other in slightly acid medium. Reference to table 2 will show the marked decrease in viscosity and  $p_H$  value that occurred after incubating pneumonic sputum for from

TABLE 2—*Viscosity and Hydrogen Ion Values of Pneumonia Sputum*

Sputum	Comment	Group of Pneumo coccus	Viscosity (Compared with Water)	$p_H$		
				Plain	After Bubbling CO <sub>2</sub> for 15 Minutes*	After Bubbling Air for 15 Minutes
1 Jan 14, 1931	After 24 hr in in cubator	1	96	7.65	6.80	7.65
			1	5.64	5.45	5.55
2 Jan 10, 1931	After 24 hr on ice After 24 hr in in cubator	1	"Very viscid"	7.47	6.57	7.47
			"Very viscid"		7.16	7.48
			"Flows readily"		5.92	6.22
3 Jan 20, 1931	After adding 1/15 its volume of dilute mercuric chloride solution against bacteria and 24 hr in incubator	1	30	7.40	6.55	
			2	6.95	6.025	

\* Carbon dioxide bubbled before incubation only

eighteen to twenty-four hours at body temperature. The decrease in viscosity of one specimen of pneumonic sputum from 96 to 1 and the decrease in  $p_H$  value are interesting. A marked decrease in  $p_H$  value is a factor unfavorable to the growth of pneumococci.

The "crisis" of pneumonia may indicate sufficient liquefaction of the intrapulmonary exudate to allow beginning ingress of air into the finer bronchi and alveoli and beginning pouring out of the lung of its liquefied matter—the volume of sputum is increased after crisis, as a rule. It is, of course, commonly accepted that a variable quantity of alveolar exudate is absorbed from the lung after crisis. The beginning re-aeration and drainage could give clinical relief in the same manner that the opening of even a relatively small focus of pus or an abscess elsewhere in the body can give relief. With the liquefaction of exudate by enzymes and drainage of the lung, the virulence of those microbes

which have survived destruction may be greatly reduced by the unfavorable environment. This concept is in keeping with the principles of drainage of other organs in the body, and can be applied to postoperative atelectasis, postoperative pneumonia and lobar pneumonia. In the lung, as with other organs, besides the local focus of infection there are general symptoms, which in pneumococcic atelectasis consist of toxicity and bacteremia. To combat the disease and overcome the general symptoms one must at least attack the focus of infection.

Those who would deny the mechanism of pulmonary drainage and recovery from pneumonia which has been described may invoke the idea of a formation of antibodies which overcome the infection. But, so far as we know, the existence of antibodies at the time of crisis is by no means constant. If such antibodies are always present, it is difficult to explain the susceptibility to pneumonia which a previous attack may confer. What is more difficult to understand is the resolution of one lobe and shortly afterward a new involvement of another lobe. We have previously shown the marked impairment of capillary circulation both in atelectatic and in pneumonic lungs, and it is difficult to see how sufficient antibodies could effectively enter the alveolar exudate. There is no doubt that the biochemistry of pneumonic exudate needs further study so that there may be an established basis on which to treat the disease directly at its focus.

To ignore the interrelation of postoperative atelectasis, postoperative pneumonia and lobar pneumonia as types in the syndrome of pneumococcic bronchial obstruction is to close our eyes to the possibility of rational therapy. Contrariwise, keeping this view in mind, we can begin to see the reason for therapeutic hyperventilation with carbon dioxide, which is now more commonly employed in postoperative routine, in carbon monoxide asphyxia and in lobar pneumonia. The aim of carbon dioxide therapy is to overcome the acapnia (carbon dioxide deficiency) caused by rapid, shallow breathing, to maintain or open the airways of the lung and to exert an antagonistic biochemical effect on the growth of pneumococci. On the latter point, further data will be published in a forthcoming paper.

As with other pathologic states, the prevention is better than the cure. The lung is normally one of the best drained organs of the body, but once bronchial obstruction occurs, it is apt to be the most poorly drained. Under normal conditions, it maintains its health in spite of the inhalation of countless microbes, irritating gases and particles of matter because its airways are kept open by various means: by the constant vigil of the cough reflex, by adequate ventilation, by the constant washing out of mucus, and by the ciliary epithelium and possibly by the rhythmic peristaltic action of bronchi—all of which are means to keep the bronchi

open and prevent obstruction and absorption of air with the ever-present danger of bacterial growth. Other microbes, when concerned with bronchial obstruction, may cause pyogenic or putrid abscess or gangrene.

In cases of pneumococcic bronchitis, repeated inhalations of mixtures of oxygen and carbon dioxide certainly constitute an excellent preventive and often curative treatment. When chill, elevation of temperature, toxic general symptoms, increased dyspnea and cyanosis, which indicates bronchial obstruction, are present, nothing is more efficient than bronchoscopic reestablishment of the patency of the bronchi. This measure, when early applied, gives gratifying results. If we can induce internists to give a fair trial to this physiologically, experimentally and clinically rational and innocuous method, instead of allowing the disease to establish itself unhampered, we shall have accomplished a great deal. Our general conception of the rôle of bronchial obstruction in pulmonary disease is offered in the accompanying outline.

Bronchitis without bronchial obstruction = simple bronchitis

Bronchial obstruction	{ Small bronchi or bronchioles	{ "Plug"* infected with pneumococci of low virulence	= patchy atelectasis
		{ "Plug" infected with highly virulent pneumo- cocci or other microbes	= bronchopneumonia
		{ "Plug" infected with pyogenic organisms or anerobes	= abscess or gangrene
	{ Bronchi of larger size	{ "Plug" infected with microbes of low viru- lence	= lobar or massive atelectasis
		{ "Plug" infected with highly virulent pneumo- cocci	= lobar or massive pneumonia
		{ "Plug" infected with pyogenic organisms or anerobes	= abscess or gangrene

\* "Plug" refers to a variable column or mass of fluid or semifluid, mucoid or fibrinous secretion or exudate, and must not be taken to mean a corklike type of occlusion at one point in the bronchial tree.

#### SUMMARY AND CONCLUSIONS

The part played by bronchial occlusion in the pathogenesis of neonatal or postnatal atelectasis and pneumonia, postoperative atelectasis and pneumonia and lobar pneumonia has been pointed out. The agent of such obstruction may vary, but when the obstruction is complete, the end-result is the same—atelectasis. Outside of amniotic fluid or fetal epithelial cells in the new-born infant, foreign bodies, intra-bronchial or extrabronchial tumors and lesions of the bronchial walls, the agent that most frequently causes bronchial occlusion and the resulting varieties of atelectasis is viscid sputum or exudate.



In lobar or massive postoperative atelectasis, pneumococci, especially group IV, are always present in the sputum. Similarly, lobar pneumonia is almost always associated with pneumococci. This incidence is explicable on the basis of the type of exudate which pneumococci produce in both instances—an exudate viscid enough to occlude a lobar bronchus and cause air absorption and atelectasis. In contrast to lobar atelectasis and lobar pneumonia, lobular atelectasis and lobular pneumonia are usually associated with other organisms, such as staphylococci, streptococci, *Bacillus influenzae*, etc. In nine cases of lobar pneumonia which were treated by bronchoscopy, the bronchus to the affected lobe was always found occluded with exudate. This conception offers a clear explanation of the “lobar” distribution of “lobar pneumonia.”

By physical and roentgen signs or even by the gross pathologic appearances it may be impossible to distinguish postoperative atelectasis, postoperative pneumonia and lobar pneumonia. In a general way, the clinical toxicity is proportionate to the virulence of the pneumococcus concerned. In lobar pneumonia there is a more marked degree of pneumococcal cellulitis and alveolar exudation, factors which may make the underlying or basic atelectasis less evident in the gross pathologic and roentgen pictures.

Experimentally, instillation of human pneumonic sputum into the bronchi of animals produced either evanescent symptoms or the clinical and roentgen pictures of lobar or massive atelectasis. Some of the latter cases went on to spontaneous recovery, others terminated fatally. Presumably the virulence of the pneumococcus concerned was the factor determining the outcome. The toxic or fatal conditions in this group were clinically comparable to lobar pneumonia, whereas the less toxic ones in which recovery occurred were clinically comparable to lobar or massive atelectasis. In man, the same difficulties are encountered, and the differential diagnosis between postoperative atelectasis, postoperative pneumonia and lobar pneumonia usually rests largely on the factor of toxicity, when the other symptoms and signs run closely parallel.

The purest types of atelectasis are represented by the condition of the normal fetal lung before respiration is instituted. After respiration has started, the inspiration of amniotic fluid or fetal epithelial cells (dermal) may cause a sterile atelectasis which when infection with micro-organisms has occurred can progress to lobar pneumonia.

The clinical toxicity of postoperative atelectasis, postoperative pneumonia and lobar pneumonia depends on the virulence of the pneumococcus concerned in the exudate causing bronchial obstruction. Absorption of alveolar gases and atelectasis occur with a spread of the infection toward the alveoli. The degree of shift of the heart and mediastinum and that of elevation of the diaphragm are inversely proportional to the amount of alveolar exudate, and this accounts for the less marked roent-

gen signs of atelectasis in lobar pneumonia, although there are cases in which the roentgen signs in pneumonia are the classic signs of atelectasis, especially in children

In the light of the theory given, if the occluding agent has been a septic foreign body or a piece of tonsillar tissue, atelectasis can be followed by anaerobic infection with necrosis, gangrene or anaerobic abscess

The symptom complex in pneumococcal bronchial obstruction is variable. What are apparently different clinical conditions should be grouped as different phases of one and the same syndrome. The underlying or basic pathologic condition is atelectasis, but the clinical aspect depends on the size of the occluded part of the lung, the duration of the bronchial occlusion, the type and virulence of the infecting micro-organism, the character and the amount of the alveolar exudate and the complications which may arise. Keeping the etiologic identity of these clinical conditions, which have usually been considered basically different, in mind, one is better equipped to recognize and to treat properly the disease complex as a definite but variable entity—the syndrome of pneumococcal bronchial obstruction

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## BOOK REVIEWS

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**Outline of Preventive Medicine for Medical Practitioners and Students**  
Prepared under the auspices of the Committee on Public Health Relations,  
New York Academy of Medicine Twenty-four contributors Editorial  
Committee Frederic E. Sondern, Charles Gordon Heyd and E. H. L. Corwin  
Second edition Price, \$5 Pp. XVII + 462 New York Paul B. Hoeber,  
Inc., 1932

The first edition of this book was published in 1929. It was reviewed in *The Journal of the American Medical Association* (93:1585 [Nov. 16] 1929). The volume was composed mainly of a series of articles by specialists written in an attempt to advise and instruct the general practitioner in matters concerning preventive medicine. Certain of the chapters were criticized as being fragmentary and vague or hurried. In general, however, the book received favorable comment. It appeared to have a praiseworthy aim and, in spite of various shortcomings, to give promise of being serviceable to the medical profession by directing attention to the fundamental obligation of the physician to aid in the prevention of disease.

That the book has fulfilled a useful purpose is evidenced by the publication of a second edition within such a short space of time. The second edition is sixty-four pages longer than the first and contains four new chapters. One chapter on industrial disease which appeared in the first edition has been deleted.

The body and the appearance of the book are much as when it first appeared, except for occasional new paragraphs which have been added here and there to amplify or to modernize certain topics. Undulant fever, for example, is now considered as being largely a preventable disorder through pasteurization of infected milk, and the preventable aspects of tularemia and psittacosis are discussed. Rabies receives considerably more space than it was given at first. No mention is made in either edition of the importance of cinchophen and allied substances in causing a preventable form of acute yellow atrophy of the liver.

Dr. Bronson Crothers' name is misspelled as Crowthers in both printings. A typographic error of this sort, occurring twice, arouses the suspicion of possible carelessness for the manner in which the references that are quoted have been verified.

The chapters that have been added deal with preclinical medicine and with hygiene, the prevention of oral disease, medical service in industry and the relation of the private physician to the health authorities. Of these, the first describes how physicians can sensibly instruct their patients who are not ill in the art of keeping well, the second stresses the importance of dental care and mouth hygiene, the third tells of the work of the present-day industrial physician, and the fourth summarizes the scope of the modern public health department, emphasizing the point of view that the various activities of public health authorities do not invade the field of the private practitioner but, rather, stimulate an increasing demand for his services.

On the whole, the book continues to make pleasant reading. The editors, in introducing it, remark that there evidently is a need for a book of this character. They suggest that subsequent editions describing important new conquests of disease will be published from time to time. Each succeeding volume of the series should be of increasing value, interest and completeness.

**Lehrbuch der inneren Medizin** By G. von Bergmann, F. Stroebe, R. Doerr, H. Eppinger and others. In 2 volumes. Price, 49.80 marks. Pp. 1,650, with 276 illustrations. Berlin: Julius Springer, 1931.

In accordance with the more modern trend, this textbook is written by a group of authors. A number of the writers, it will be noted, are among the outstanding

clinicians of Germany As one would suspect, this work is detailed and is written in scholarly fashion It is probably to be recommended more as a reference book than as a textbook

Volume I is divided as follows (1) The introduction by Dr R Siebech is a discourse on the art of medicine and also includes outlines for history taking and physical examination, (2) Infectious Diseases, by Dr R Doerr and Dr R Staehelin, (3) Diseases of the Cardiovascular System and Mediastinum, by Dr P Morawitz, (4) Diseases of the Respiratory System, by Dr S J Thannhauser, (5) Diseases of the Digestive Tract, by Dr W Stepp, (6) Diseases of the Liver and Biliary Tract, by Dr G v Bergmann with Dr F Stroebe

Volume II is divided as follows (1) Diseases of the Urinary Tract, by Dr H Strausz, (2) Metabolic Disorders, by Dr L Lichtwitz, (3) Diseases of the Organs of Internal Secretion, by Dr Hans Eppinger, (4) Diseases of the Blood and Blood Forming Organs, by Dr A Schittenhelm, (5) Diseases of the Muscles, Bones and Joints, by Dr S J Thannhauser, (6) Diseases of the Nervous System, by Dr F Hiller, (7) The Neuroses, by Dr R Siebech, (8) Toxicology, by Dr P Morawitz, (9) Diseases Due to Physical Agents, by Dr S Katsch, (10) Injuries Due to Radioactive Rays, by Dr R Schittenhelm, (11) General Therapeutic Measures, by Dr L Lichtwitz

This work is more extensive than our most popular medical textbooks, but the general plan in the presentation of the various diseases is similar Rare diseases are printed in small type Considerable emphasis has been placed on pathology and physiology The material is for the most part original and is based on the experiences of the authors Numerous references are made to the literature throughout the text, and a bibliography appears at the end of each section However, there are few or no references to other than German literature One of the fine features of this textbook is the abundance of illustrations This is especially true in the sections on gastro-intestinal, cardiac and thoracic diseases Here are used clear reproductions of the roentgenograms illustrating each of the diseases under discussion The section on neurology contains numerous photographs and charts Methods of treatment are those in use on the continent

Teachers of medicine will find this book a valuable source of information

**Manipulative Surgery** By A S Blundell Bankart, M A, M Ch (Cantab), F R C S Price, 7 shillings, 6 pence Pp 162 London Constable & Co, Ltd, 1932

This is an unusual book, covering a subject which surgeons shun and of which most of them are woefully ignorant

The introductory section deals with general subjects, such as anatomic considerations, sprains and adhesions, postural activity of muscles, chronic strain, joint subluxations, arthritis, the general principles of manipulation, anesthetics, the limitations of, and the results that can be expected from, manipulating various types of conditions

The subsequent sections deal specifically with conditions involving the feet, the knees and hips and muscles and tendons in the lower extremities, spine and pelvis, and the fingers, hands and wrists, elbows and shoulders

There are three outstanding chapters, which alone make reading this book profitable, those dealing with the foot, knee, spine and pelvis The meaning, mechanism and treatment of "foot strain," as presented, will, I warrant, give most surgeons an entirely new aspect on this subject The "derangements of the knee," particularly displaced semilunar cartilages and especially the pathology and treatment are clearly presented Pains in the lower region of the back are differentiated, and indications for and methods of manipulation are prescribed, again a subject in which the average surgeon has limited knowledge

The manipulation of joints properly requires a tremendous amount of experience and absolute confidence in one's own ability to do it Most men would hesitate to apply as great a force to the joints as the author claims is necessary for good results, for fear of overdoing it and producing untoward results

One connected with a large clinic, where opportunity for constant application of these principles is afforded, doubtless would find this book of much practical value. The average physician would change many of his ideas about these conditions of the joint, but would probably have limited opportunity to make use of the treatments prescribed.

**A Handbook of Experimental Pathology** By George Wagoner, M D, Associate in Pathology, and R Philip Custer, M D, Associate in Research Pathology, University of Pennsylvania, Philadelphia. Price, \$4. Pp 160, with 6 tables and 23 figures. Springfield, Ill. Charles C Thomas, 1932.

Prof Edward B Krumbhaar, in introducing this volume, aptly terms it a pioneer effort. The book purports to be a modest handbook of experimental pathology based on the course in this subject given to the second year students of medicine in the University of Pennsylvania Medical School. It appears to achieve its aim.

The first chapter deals with technic. In it is found a good description of how to care for the various kinds of animals that may be utilized in experimental work, how to house and feed them, metabolism cages and operating tables, anesthetics and their dosage and methods of use, ways for obtaining specimens, and, finally, a table of normal blood and blood chemical findings for the various species. This introductory chapter is written sanely and, above all, emphasizes the fact that to carry out acceptable animal experimentation the perfection of surgical care is essential.

The ensuing chapters describe standard methods for producing and studying a great many lesions of different kinds. A wide range of subjects is covered, including experiments dealing with general pathology, the special pathology of the various systems of the body, the vitamins and the phenomena of hypersensitivity. Thus there is condensed into the body of the book a description of how to reproduce in animals most of the important occurrences in man with which a beginning pathologist must become familiar.

A textbook of this sort is so interesting and timely that the authors are to be congratulated on having put it together. Medical schools other than its alma mater will be quick to appreciate its usefulness.

**The Cardiac Output of Man in Health and Disease** By Arthur Grollman, Ph D, M D, Associate Professor of Physiology, Johns Hopkins University. Price, \$4. Pp 325. Springfield, Ill. Charles C Thomas, 1932.

As is suggested by the title, this monograph discusses cardiac output in a most comprehensive fashion. It includes a bibliography of 483 references.

A history of the early attempts to estimate cardiac output is followed by an account of the more important investigations that have led to the establishment of the direct and indirect methods for the determination now in use. Several indirect methods are compared in regard to their relative accuracy, and the advantages and disadvantages of each one are analyzed. The general principles and technical details of the acetylene method advocated by the author are described.

The effect of various physiologic factors which may influence cardiac output is emphasized. The section of the book relating to this matter is perhaps the most notable part of the volume, since the author establishes by his own method, in a series of carefully executed determinations, a set of normal values essential to the interpretation of results obtained under abnormal conditions. The effect on cardiac output of different drugs, including various endocrine gland extracts, and of certain diseases is dealt with, and, finally the author attempts to correlate cardiac output with other physiologic functions.

The entire study is presented in a succinct, lucid and stimulating fashion. Certainly it will interest clinicians as well as physiologists, particularly those clinicians who are devoting attention to the investigation of problems related to the circulatory system.

## CATAPHORETIC VELOCITY OF STREPTOCOCCI AS ISOLATED IN STUDIES OF ARTHRITIS

EDWARD C ROSENOW, M D

ROCHESTER, MINN

One of the reasons why the importance of streptococci in the etiology of rheumatic fever and various other forms of arthritis, especially chronic infectious arthritis, is not sufficiently recognized is the fact that bacteriologists have been too much concerned with differences in cultural reactions and not enough with the peculiar infecting power of the streptococci isolated, especially immediately after isolation. The diseases comprising the arthritic group, generally considered as being due to streptococci, are so different in their clinical and pathologic manifestations, and the cultural properties of streptococci are so variable,<sup>1</sup> that the requirements stressed by some<sup>2</sup> that all streptococci isolated must have identical cultural reactions to be of significance is fallacious. In a long series of experiments, I have shown that the streptococci isolated in cases of rheumatic fever<sup>3</sup> and chronic infectious arthritis,<sup>4</sup> irrespective of whether they are green-producing, indifferent or slightly hemolytic, possess on isolation peculiar localizing and disease-producing powers. The conditions at hand in the patients from whom the various types were isolated were often closely simulated in inoculated animals. The three types of streptococci (green-producing, slightly hemolytic and indifferent) which I isolated from tonsils, blood, joints,

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From the Division of Experimental Bacteriology, the Mayo Foundation

1 Rosenow, E C. Transmutations Within the Streptococcus-Pneumococcus Group, *J Infect Dis* **14** 1 (Jan) 1914. Todd, E W. The Conversion of Hemolytic Streptococci to Non-Hemolytic Forms, *J Exper Med* **48** 493 (Oct) 1928.

2 Birkhaug, K E. Rheumatic Fever. Bacteriologic Studies of a Non-Methemoglobin-Forming Streptococcus with Special Reference to Its Soluble Toxin Production, *J Infect Dis* **40** 549, 1927. Clawson, B J. Studies on the Etiology of Acute Rheumatic Fever, *ibid* **36** 444, 1925. Small, J C. The Bacterium Causing Rheumatic Fever and a Preliminary Account of the Therapeutic Action of Its Specific Antiserum, *Am J M Sc* **173** 101 (Jan) 1927. Swift, H F, Derick, C L, and Hitchcock, C H. Rheumatic Fever as a Manifestation of Hypersensitiveness (Allergy or Hyperergy) to Streptococci, *Tr A Am Physicians* **43** 192, 1928.

3 Rosenow, E C. The Etiology of Acute Rheumatism, Articular and Muscular, *J Infect Dis* **14** 61 (Jan) 1914.

4 Rosenow, E C. Etiology of Arthritis Deformans, Preliminary Note, *J A M A* **62** 1146 (April 11) 1914.



muscles and regional lymph nodes in cases of rheumatic fever <sup>5</sup> (isolated since from the blood in a high percentage of cases of Cecil, Nicholls and Stainsby <sup>6</sup>), besides having marked affinity for joints (66 per cent of 71 animals inoculated), had marked affinity for the heart (in 46 per cent endocarditis developed, in 44 per cent, myocarditis). Similar strains, isolated from atria of infection, excised tissues and regional lymph nodes draining arthritic joints in cases of chronic infectious arthritis <sup>7</sup> also had marked affinity for joints (53 per cent of 1,447 animals given injections) but little affinity for the heart (in only 5.5 per cent of animals given injections did lesions of the cardiac valves develop, and less than 1 per cent had lesions of the myocardium).

Indeed, the method of intravenous injection of the streptococcus as obtained from various atria of infection and the making of cultures from the tissue affected has served to separate the saprophytes from the pathogens and has served to isolate the probable causative streptococcus in a long series of cases of chronic infectious arthritis and other diseases <sup>7a</sup>. Serologic studies with hyperimmune serums prepared in the horse from representative strains of streptococci isolated in studies of chronic infectious arthritis have shown that most of the strains thus isolated are immunologically alike <sup>8</sup>. Agglutination with the serum of the patient, however, was not sufficiently striking to be of constant diagnostic significance <sup>8</sup>. The method of intravenous injection of freshly isolated organisms, too, has its limitations. It is costly, time-consuming and difficult, and is not always successful. Some investigators <sup>9</sup> have had difficulty in corroborating my results. To prove a causal relationship of streptococci in studies of chronic infectious arthritis by making cultures of fluid from the joints is impossible, because cultures are nearly always negative <sup>4</sup>. The method of making cultures from excised articular tissues and regional lymph nodes, although more often positive,<sup>10</sup> is painful and impracticable on a large scale. Cutaneous tests for hypersensitiveness, attempts at desensitization with antigens prepared from streptococci, relief from symptoms following removal of

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5 Rosenow, E. C. The Newer Bacteriology of Various Infections as Determined by Special Methods, *J. A. M. A.* **63** 903 (Sept. 12) 1914.

6 Cecil, R. L., Nicholls, Edith E., and Stainsby, W. J. Bacteriology of the Blood and Joints in Rheumatic Fever, *J. Exper. Med.* **50** 617 (Nov.) 1929.

7 Rosenow, E. C. (a) Focal Infection and Elective Localization, *Internat. Clin.* **2** 29 (June) 1930, (b) footnotes 4 and 5.

8 Rosenow, E. C. Serologic Specificity of Streptococci Having Elective Localizing Power as Isolated in Various Diseases of Man, *J. Infect. Dis.* **45** 331, 1929.

9 Valentine, Eugenia, and Van Meter, Martha. The Localization of Streptococci in the Tissues of Rabbits, *J. Infect. Dis.* **47** 56, 1930.

10 Margolis, H. M., and Dorsey, Anna H. E. Chronic Arthritis, *Bacteriology of Affected Tissues*, *Arch. Int. Med.* **46** 121 (July) 1930. Rosenow (footnotes 4 and 5).

foci of infection and the use of vaccines prepared from streptococci that have been shown to have elective localizing power, although of great value in some cases,<sup>11</sup> cannot solve the problem of etiology. Isolation of streptococci from the blood, so successfully accomplished by Cecil, Nicholls and Stainsby,<sup>12</sup> and corroborated by me in several groups of cases but not in others,<sup>10</sup> although of great value if the results are positive, also has its limitations. The successful agglutination experiments conducted by these workers with the serum of patients and the production of arthritis in animals with their typical strains are the most consistent proof yet produced of etiologic relationship, but here too there are disturbing factors. Their strains are hemolytic and extremely sensitive to agglutination, and the streptococci which we and others<sup>13</sup> have isolated in studies of chronic infectious arthritis and myositis are chiefly green-producing or indifferent and usually resist agglutination by the serum of the patient.<sup>8</sup> The need for further study of the problem by new methods, especially for identification of the streptococci and proof of their etiologic relationship in acute and chronic infectious arthritis and in "rheumatic" arthritis, is apparent.

In a preliminary report, Jensen and I<sup>14</sup> have shown that streptococci having elective localizing power, as isolated from foci of infection in studies of encephalitis and arthritis, have characteristic cataphoretic velocity, and that the respective serums have specific potential lowering effects on these streptococci. It is my purpose in this report to describe the technic and to record results obtained in a further study of streptococci isolated in cases of arthritis.

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11 Rosenow, E. C., and Nickel, A. C. Results in Various Diseases from Elimination of Foci of Infection and Use of Vaccine Prepared from Streptococci Having Elective Localizing Power, *J. Lab. & Clin. Med.* **14** 504 (March) 1929.

12 Cecil, R. L., Nicholls, Edith E., and Stainsby, W. J. The Bacteriology of the Blood and Joints in Chronic Infectious Arthritis, *Arch. Int. Med.* **43** 571 (May) 1929, footnote 6.

13 Haden, R. L. The Elective Localization of Bacteria in Peptic Ulcer, *Arch. Int. Med.* **35** 457 (April) 1925. Meisser, J. G., and Brock, Sam. A Clinical and Experimental Study in Chronic Arthritis, *J. Am. Dent. A.* **10** 1100 (Dec.) 1923. Moench, L. Mary. The Relationship of Chronic Endocervicitis to Focal Infection with Special Reference to Chronic Arthritis, *J. Lab. & Clin. Med.* **9** 289 (Feb.) 1924. Nakamura, T. A Study on Focal Infection and Elective Localization in Ulcer of the Stomach and in Arthritis, *Ann. Surg.* **79** 29 (Jan.) 1924. Nickel, A. C. The Localization in Animals of Bacteria Isolated from Foci of Infection, *J. A. M. A.* **87** 1117 (Oct. 2) 1926. Rosenow (footnotes 4, 5 and 7). Rosenow, E. C., and Ashby, Winifred. Focal Infection and Elective Localization in the Etiology of Myositis, *Arch. Int. Med.* **28** 274 (Sept.) 1921. Valentine and Van Meter (footnote 9).

14 Rosenow, E. C., and Jensen, L. B. Elective Localization and Cataphoretic Potential of Streptococci. Preliminary Report, *Proc. Soc. Exper. Biol. & Med.* **27** 442, 1930.

## METHOD OF STUDY

The method of obtaining material for cultures, and the preparation of cultures for study of cataphoretic velocity and inoculation of animals, were essentially like those used in work on elective localization. The materials from the nasopharynx, tonsils, pyorrheal pockets about the teeth, prostate gland or uterine cervix and fluid and tissue from joints were plated as a routine on blood-agar and used for inoculation of tall columns of previously warmed dextrose-brain broth. Material from the apices of pulpless teeth was used for inoculation of tall columns of dextrose-brain agar in addition, because the streptococci from these regions are anaerobic and will not grow on blood-agar plates in primary culture. Cultures from the stool were made by plating on blood-agar plates in series, and single colonies of streptococci were fished and used for inoculation of the test medium, dextrose-brain broth, for studies of cataphoretic velocity. The cultures were incubated at 35 C for from eighteen to twenty-four hours, rarely longer. If the growth on the primary blood-agar plates revealed a preponderance of colonies of streptococci, and if the culture in brain broth had grown with diffuse turbidity, without formation of gas, which was the rule, about 2 cc was poured into scrupulously clean test tubes. This amount was centrifugated just sufficiently to clear the broth. The supernatant fluid was then thoroughly drained off, and the sediment was suspended as evenly as possible in 12 cc of distilled water, and this, after it had stood for a short time to allow bubbles of gas to escape, was poured into a Northrop-Kunitz-Mudd cataphoresis apparatus. It was found that when the growth on the primary blood-agar plate revealed a great preponderance of colonies of streptococci, and the culture in dextrose-brain broth had grown with diffuse turbidity, and without formation of gas, film preparations and platings of dextrose-brain broth always revealed pure or nearly pure cultures of streptococci that grew in short chains. Hence, these methods of verification, although used in each new disease studied until the characteristic type of velocity had been established, were omitted in routine work. If the primary blood-agar plate revealed a preponderance of staphylococci, which occurred sometimes in work with nasopharyngeal swabbings, but almost never in work with cultures from apices of pulpless teeth and never in cultures from affected joints of animals that had received injections, or if the plates revealed bacilli and the dextrose-brain broth culture grew with formation of gas, film preparations and platings were always made to verify the studies of cataphoresis. However, even if the plates revealed bacilli and the dextrose-brain broth culture grew with formation of gas, a great preponderance of streptococci having characteristic velocities was the rule. The determinations of velocity were made at approximately constant voltage (120 volts) and temperature (20 to 24 C), and a stop watch was used to note the time required for each of from ten to twenty organisms, depending on the evenness of their rate of migration, to traverse 50 microns, the unit distance. The time required in seconds and fourths of seconds for each organism to traverse this unit distance was recorded, and from this the cataphoretic velocity was determined in terms of microns per second, per volt per centimeter, according to the formula

$$\text{Cataphoretic velocity} = \frac{50 \text{ microns}}{\text{time in seconds} \times \text{potential gradient (7.8 volts per cm)}}$$

For example, most streptococci derived from patients with chronic infectious arthritis traverse the unit distance of 50 microns in the cataphoretic cell in three seconds, and the effective potential gradient as the cell was used was found to be 7.8 volts per centimeter by actual measurement, hence, microns per second, per volt per centimeter equals  $\frac{50}{3 \times 7.8}$ , or 2.13

TABLE 1—*Cataphoretic Velocity of Streptococci as Isolated in Studies on Arthritis*

TABLE 1—Cataphoretic Velocity of Streptococci																									
Diseases	Source of Streptococcus	Strains										Cultures										Streptococci Timed			
		Per Cent										Per Cent										Number	Neurotropic	Arthro tropic	Other
		Number	Neurotropic	Arthro tropic	Normal	Rhino tropic	Pharyngo- tropic	Broncho tropic	Other	Number	Neurotropic	Arthro tropic	Normal	Rhino tropic	Pharyngo- tropic	Broncho tropic	Other								
Chronic infectious arthritis cultures from nasopharynx, tonsils, teeth, prostate gland or uterine cervix	A* J*	189 31	5 0	70 87	10 10	3 0	4 0	12 0	6 0	120 66	11 2	64 83	12 7	0 0	1 1	1 2	1 0	1,082 600	19 15	60 65	20 20	1,082 600	19 15	60 65	20 20
Chronic infectious arthritis cultures from teeth, not included in larger series	A	79	13	63	16	0	0	0	0	75	11	73	11	0	1	1	0	1,009	25	58	17	1,009	25	58	17
Acute infectious arthritis cultures from nasopharynx	A J	8 11 3	0 0 0	88 100 100	12 0 0	0 0 0	0 0 0	0 0 0	0 0 0	19 13 5	0 0 0	89 100 100	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	211 85	10 6	76 63	14 11	211 85	10 6	76 63	14 11
Arthritis old cultures after long cultivation on artificial mediums	A	16	0	69	25	6	0	0	0	17	0	65	20	6	0	0	0	231	23	56	21	231	23	56	21
Neutromyositis with or without arthritis cultures from nasopharynx, tonsils or teeth	A J	10 2	50 50	40 50	0 0	0 0	0 0	10 0	0 0	48 18	52 39	46 50	0 0	0 0	0 0	2 11	0 0	502 335	50 40	50 59	20 21	502 335	50 40	50 59	20 21
Epikemic encephalitis cultures from nasopharynx, tonsils, teeth, prostate gland or uterine cervix	A B*	75 15	96 93	0 0	4 7	0 0	0 0	0 0	0 0	98 34	96 94	1 0	3 6	0 0	0 0	0 0	0 0	1,418 728	65 57	12 16	23 27	1,418 728	65 57	12 16	23 27
Tuberculosis of bones and joints cultures from nasopharynx	A	14	0	14	64	8	14	0	0	14	0	14	64	8	14	0	0	135	22	47	11	135	22	47	11
Normal persons cultures from nasopharynx	A	345	1	11	76	3	4	1	3	345	1	11	76	3	4	1	3	3,574	25	46	29	3,574	25	46	29
Note: Strains that had been given injections, B = brains of animals that had been given injections																									

\* A = attitud of infection of patient, I = joints of animals that had been given injections, B = brains of animals that had been given injections

The operator in most instances was unaware of the diagnosis in the cases in which the culture or cultures were obtained. Cultures of material from atria of infection of patients having different diseases, and from old cultures, were purposely included on the same day in order to be sure that the results were reliable.

In table 1 and in the text, cultures containing a preponderance of streptococci with a velocity of 2.29, 2.13 or 2 microns per second, per volt per centimeter, are designated as arthrotropic because streptococci of these velocities occur in great preponderance in cases of arthritis. Those with a velocity of 3.56, 3.2 or 2.91 and those with velocities of 1.68, 1.6 or 1.52 microns per second, per volt per centimeter, are designated as poliomyelitic or neurotropic because these velocities

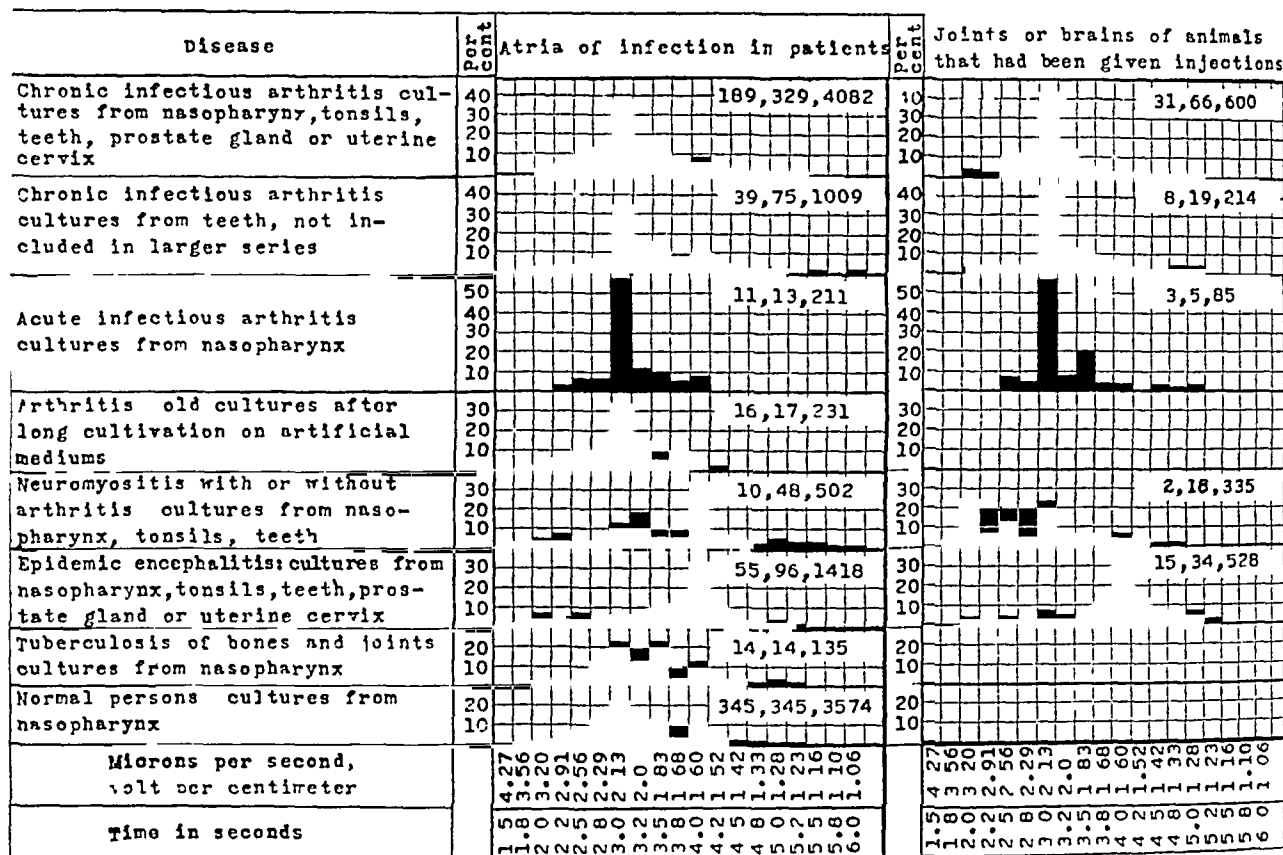


Fig 1—Cataphoretic velocity of streptococci as isolated in studies of arthritis. The numbers inserted in the right upper corner of each graph indicate, respectively, the number of strains, cultures and streptococci timed in each group studied.

predominate in poliomyelitis, encephalitis and other diseases of the nervous system. Those with a distribution of velocities like those of streptococci from throats of normal human beings in times free from epidemics, in which there is a moderate preponderance of streptococci having a velocity of 2.29, 2.13 or 2 microns per second, per volt per centimeter, are designated as normal. Those with a velocity of about 2.56 microns per second, per volt per centimeter, are designated as rhinotropic, because this is the predominating velocity of streptococci isolated from the nasopharynx in cases of acute rhinitis. Those with a velocity of about 1.83 microns per second, per volt per centimeter, are designated as pharyngotropic, because this

is the predominating velocity of streptococci isolated from the nasopharynx in cases of pharyngitis or sore throat. Those with a velocity of chiefly 183, 16, 142 or 128 microns per second, per volt per centimeter, are designated as bronchotropic, because streptococci with such velocities are commonly at hand in cases of influenza, affecting chiefly the throat and bronchi, and associated with marked constitutional reactions.

The number of streptococci the velocity of which was determined in individual strains and cultures was approximately the same in the different groups. The percentage incidence of the different velocities, as shown in figures 1 and 2, was determined by dividing the number of streptococci that had these different velocities by the total number of streptococci timed in each group.

In the course of previous studies, specific agglutination was sometimes obtained with the serum of the patient, the streptococci isolated in studies of the disease

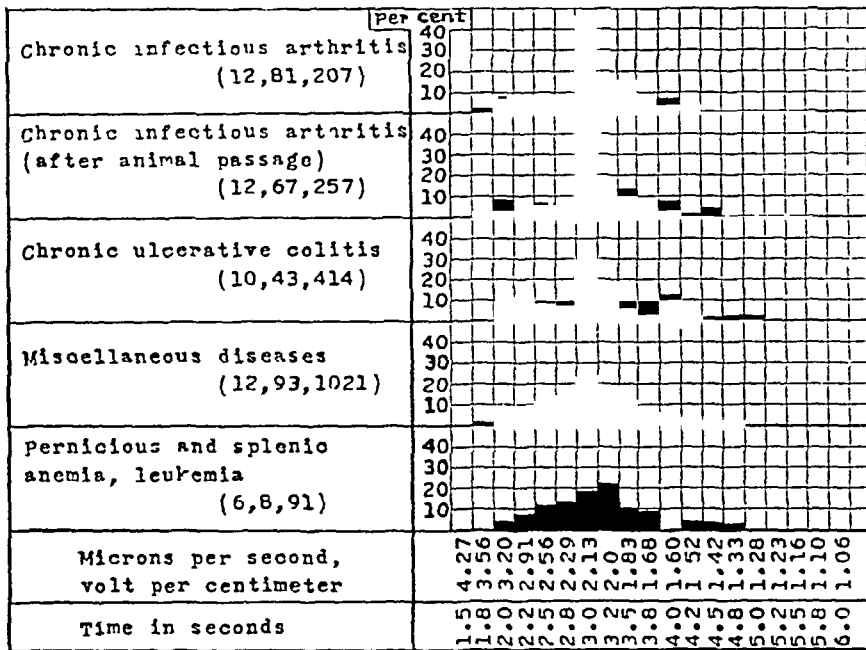


Fig 2—Cataphoretic velocity of streptococci as isolated from the stool in cases of chronic infectious arthritis and other diseases. The figures in parenthesis indicate, respectively, the number of strains, cultures and streptococci timed in each group studied.

with which the patient was suffering being used, the streptococci were agglutinated in high dilution in the corresponding hyperimmune horse serums, but the agglutination in serum from patients was not constant enough to be of unmistakable diagnostic value. It occurred to me that possibly the serum of the patient might lower specifically the cataphoretic velocity of the streptococcus in question in sufficiently high dilution for the evidence thus obtained to be of unquestioned value. Accordingly, a series of experiments was undertaken to determine the most reliable method by varying the density of the suspensions, the electrolyte content, the duration and degree of heating of the suspensions and the method of holding constant the characteristic potential of stock suspensions of the different strains of streptococci. The following technic was adopted as most reliable and the results recorded in table 2 were obtained by its careful application.

Dilutions of serum were made as a routine, in series, in suspensions of bacteria as follows 1 to 20, 1 to 40, 1 to 80, 1 to 160, 1 to 320, 1 to 640, 1 to 1,280 and 1 to 2,560, and sometimes also 1 to 5,120 and 1 to 10,240, each tube containing 15 cc. The diluted suspensions of the respective streptococci were made from stock, dense suspensions (1,000,000,000,000 streptococci in each cubic centimeter) in glycerin (2 parts), and 25 per cent sodium chloride solution (1 part), which had been kept in the refrigerator. The dense suspensions were diluted with distilled water to about a fourth the density of dextrose-brain broth cultures, or

TABLE 2—*Specific Velocity-Slowing Effect of the Serum from Patients with Arthritis on Streptococci Isolated in Studies of Arthritis*

Serums	Streptococcal Suspensions		
	Arthritis	Encephalitis	Polomyelitis
Chronic infectious arthritis (2)*	1 1280†	1 80	1 80
Chronic infectious arthritis (3)	1 2560	1 80	1 80
Chronic infectious arthritis (2)	1 5120	1 640	
Chronic infectious arthritis (2)	1 1280	1 320	
Chronic hypertrophic arthritis (2)	1 1280	1 80	1 40
Subacute infectious arthritis	1 640	1 80	1 80
Acute arthritis	1 2560	1 40	1 80
Rheumatic arthritis (2)	1 1280	1 160	1 160
Chronic spondylitis	1 640	1 80	1 40
Chronic arthritis and myositis	1 1280	1 80	1 80
Periarthritis	1 2560	1 40	1 80
Neuromyositis and arthritis (2)	1 1280	1 640	1 320
Neuromyositis (2)	1 1280	1 320	1 80
Neuromyositis	1 640	1 80	1 40
Chronic parkinsonian encephalitis (2)	1 80	1 2560	1 80
Recurring encephalitis	1 80	1 2560	1 40
Chronic parkinsonian encephalitis	1 80	1 640	1 320
Mild chronic encephalitis	1 80	1 1280	1 40
Acute myoclonic encephalitis	1 80	1 320	1 40
Acute myoclonic encephalitis (2)	1 80	1 1280	1 40
Acute parkinsonian encephalitis	1 80	1 5120	1 2560
Acute poliomyelitis (3)	1 40	1 40	1 1280
Acute poliomyelitis	1 160	1 320	1 5120
Acute poliomyelitis	1 160	1 160	1 2560
Convalescent poliomyelitis (2)	1 80	1 80	1 2560
Convalescent poliomyelitis (2)	1 80	1 40	1 1280
Convalescent poliomyelitis	1 160	1 320	1 5120
Normal serum (2)	1 40	1 20	1 80
Normal serum (5)	1 80	1 80	1 80
Normal serum (2)	1 80	1 40	1 40
Normal serum (3)	1 40	1 40	1 40
Normal serum (2)	1 80	1 80	1 40
Normal serum (3)	1 160	1 160	1 160
Normal serum (2)	1 80	1 80	1 320
Normal serum	1 320	1 320	1 640
Normal serum	1 160	1 320	1 320

\* Figures in parenthesis indicate number of cases

† The highest dilution in which the serum had a velocity slowing effect

about 500,000,000 streptococci in each cubic centimeter. If more dilute suspensions in glycerin and salt solution were used, requiring the addition of a larger quantity of sodium chloride, or electrolyte, the suspension in water was washed once and resuspended in water. After the suspensions and serum had been thoroughly mixed, the set-up was placed first in the incubator for one hour and a half, in the oven at 52 C for two hours and then in the refrigerator over night. The following morning the tubes were inspected for evidence of macroscopic agglutination, the controls consisting of suspensions only, and each mixture, containing various amounts of serum, in turn was diluted with 14 cc of distilled water and was poured into the cataphoretic cell, and the rate of migration was determined in the usual manner.

## RESULTS

The results obtained from a study of cataphoretic velocity of the streptococci isolated from atria of infection in the different groups of cases and controls are summarized in table 1, and shown graphically in figure 1, and those isolated from the stool are shown in figure 2. The high incidence is noteworthy, in strains and cultures, of a preponderance of streptococci having arthrotropic velocity, as isolated from various atria of infection in cases of chronic infectious arthritis (63 to 100 per cent), especially after animal passage (87 to 100 per cent), a similar high incidence was noted in cases of acute infectious arthritis. These results are in sharp contrast to the almost complete absence of arthrotropic strains as isolated from atria of infection in studies of cases of epidemic encephalitis, it is also in contrast to a very low incidence of arthrotropic organisms (11 to 14 per cent) in the strains and cultures isolated from the nasopharynx in patients with tuberculosis of the bones and joints and in normal persons. After the arthritic strains had been cultured on artificial mediums for a long time they lost much of the arthrotropic velocity, and the configuration of the curve resembled closely that of streptococci from the throats of normal persons. Most interesting of all, the strains and cultures before and after animal passage, from atria of infection in the group of cases of neuromyositis, with or without arthritis, were partly neurotropic and partly arthrotropic.

The percentage incidence in the different groups of all streptococci that had arthrotropic and neurotropic velocities was in close agreement with that of the percentage incidence of strains and cultures having streptococci chiefly of these velocities. The total distribution of velocities in each of the groups studied is shown graphically in figure 1. The consistently high incidence of streptococci having arthrotropic velocity, highest in cultures made from atria of infection in acute cases of arthritis and from the joints of animals that had received injections, is well shown and is in sharp contrast with the graphs illustrating the velocity of streptococci isolated in studies of cases of encephalitis. The velocities of the streptococci isolated in cases of neuromyositis occupy an intermediate position between the velocities of streptococci isolated in studies of arthritis and those from encephalitis. The seeming discrepancy between the figures illustrating the velocities of the strains before and after animal passage in the neuromyositis group is really not a discrepancy, because the neurotropic streptococci which traverse the unit distance of 50 microns in four seconds before animal passage commonly traverse it twice as fast after animal passage and on cultivation of these strains on artificial mediums they often revert in speed by a multiple of 2. The similarity of the distribution of velocities of the arthritic strains, especially after long cultivation on artificial mediums,



and of those isolated from the nasopharynx in normal persons and in persons having tuberculosis of the bones and joints is also well shown.

The distribution of cataphoretic velocity of all streptococci timed from single colony cultures of the stool on blood-agar as subsequently grown in dextrose-brain broth is represented graphically in figure 2. The incidence of anarthrotropic velocity of the streptococci isolated in cases of chronic infectious arthritis, before and after animal passage, is extremely high. The distribution of velocities is practically normal in single colony cultures of streptococci derived from the stool in cases of chronic ulcerative colitis, miscellaneous diseases taken together, pernicious anemia, splenic anemia and leukemia. Most of the streptococci found in suspensions, made directly in distilled water, of nasopharyngeal swabbings and in pus from tonsils in cases of arthritis had arthrotropic velocity.

The serum in cases of arthritis has been found to have far greater effect in slowing the rate of migration (reduction of electric charge) of streptococci obtained in studies of arthritis than in slowing the velocity of streptococci isolated in cases of encephalitis and poliomyelitis, and in much higher dilution. In the lower dilutions of serum the streptococci isolated in cases of arthritis were rendered isopotential. In table 2 are summarized the results obtained with the serum from persons having different forms of arthritis and neuromyositis with and without arthritis, in contrast with the serum from persons having encephalitis or poliomyelitis and with that from normal persons. The suspensions of streptococci isolated in cases of arthritis, used mainly in these experiments, consisted of ten strains of green-producing streptococci isolated from the affected joints of rabbits following intravenous injection of the streptococci from various areas of infection in cases of chronic infectious arthritis. The suspensions of streptococci from persons with encephalitis and poliomyelitis were isolated either from the nasopharynx, and were used after one animal passage, or were isolated from the brain and cord of patients with encephalitis and poliomyelitis. There were twenty-four strains in the encephalitis suspension and nine strains in the poliomyelitis suspension. All three suspensions represented the growth from 0.2 per cent dextrose broth which had been preserved in very dense suspension in glycerin (2 parts) and 25 per cent sodium chloride solution (1 part) for from one to ten years. It will be noted that the serum in cases of various forms of arthritis had a slowing effect in far higher dilution on the arthritic streptococci than on the streptococci obtained in cases of encephalitis or poliomyelitis. The results of agglutination in low dilution, when positive, agreed with velocity-slowness effects, but in these experiments, as heretofore, such agglutination occurred too irregularly to be of undoubted diagnostic value. The serum in cases of neuromyositis affected most markedly

and in high dilution, the streptococci with arthrotropic velocity from patients with arthritis but affected also, moderately the streptococci from patients with encephalitis which had neurotropic velocity. The results of serum potential studies proved helpful in differential diagnosis in several cases belonging in the group of neuromyositis, in which, from clinical manifestation and roentgenograms, it was impossible to say whether the pain over the distribution of the sciatic nerve (sciatica) was due to arthritis, to sacro-iliac subluxation or to neuritis. The presence in the nasopharynx of a great preponderance of streptococci having arthrotropic velocity and a particularly marked slowing effect of the serum on arthrotropic streptococci were considered to indicate arthritis; a great preponderance of streptococci having neurotropic velocity and a marked slowing effect on neurotropic streptococci as indicating neuritis; a combination of these velocities and serum effects as indicating both arthritis and neuritis, and a normal nasopharyngeal streptococcal flora and normal velocity-reducing effect, as indicating merely mechanical impingement on the nerve roots. The serum of patients with encephalitis affected markedly, and in high dilution, the streptococci isolated in cases of encephalitis but the effect of this serum on the streptococci from patients with arthritis and with two exceptions its effect on the streptococci from patients with poliomyelitis, were no greater than that of normal serum. The serum from patients with poliomyelitis and from persons having recovered from poliomyelitis affected most markedly and in high dilution the streptococci of poliomyelitis, but this serum affected, scarcely more than normal serum streptococci from patients with encephalitis and arthritis. These specific effects are in sharp contrast to the somewhat variable but always relatively slight effect on each of the respective strains of the serum from normal persons. Results comparable to these were obtained with autogenous strains of streptococci isolated in cases of arthritis with other heterologous strains and with heated and unheated suspensions both as isolated and after preservation in the glycerin-salt solution menstruum. It made little difference whether the strains were green-producing (which was usually the case), indifferent, slightly hemolytic or markedly hemolytic on blood-agar plates. The velocity of almost all strains was specifically reduced by the serums of patients with arthritis, provided the cataphoretic velocity or potential was arthrotropic, if the strains were not arthrotropic, the serum of patients with arthritis had no more, or only a slightly greater effect than serum from normal persons.

Absorption experiments with the arthrotropic streptococci removed specifically from the serum of patients with arthritis its power of reducing velocity. In a number of cases the titer of serum increased markedly as patients recovered from relatively acute attacks of arthritis,

In addition to the striking evidence, as shown in table 1 and figures 1 and 2, of the importance of determination of the arthrotropic potential or velocity in learning the capabilities of localization in joints of streptococci isolated from patients with arthritis, it has been found that when cultures containing a mixture of streptococci, having respectively arthrotropic and neurotropic velocities are injected, a pure or almost pure culture of streptococci having arthrotropic velocity is obtained from the joints, and a pure or almost pure culture of streptococci having neurotropic velocity is obtained from the brain. This occurred in cultures obtained from a joint and the brain or from a joint or the brain of nine rabbits which had received intravenous injections of seven strains containing streptococci having neurotropic velocity. It also occurred with three other strains containing streptococci of different velocities injected intraperitoneally into one mouse and intravenously into one rabbit. The cultures from the brains of these animals were often positive, even when there were no symptoms of encephalitis during life, the cultures from the brains of normal rabbits were never positive.

A markedly arthrotropic streptococcal flora was found in the nasopharynx of each of six patients suffering from supposedly senescent arthritis. Moderately positive serum potentials against arthrotropic streptococci were demonstrated in each of three of these cases. In each of three cases of active chronic infectious arthritis, and in two of neuromyositis, the characteristic abnormal cataphoretic velocity of streptococci, as isolated from the nasopharynx, became normal coincidentally with marked improvement and the prolonged use of vaccines prepared from strains that had specific localizing power and characteristic cataphoretic velocity. The serum of each of these patients developed a marked cataphoretic velocity-slowness effect on the respective streptococci. With the return of symptoms following discontinuance of administration of the vaccine, the streptococcal flora of the nasopharynx having chiefly arthrotropic velocity, again returned. The streptococci isolated in the usual manner from the nasopharynx and other foci of infection in each of nine cases of acute rheumatic arthritis had mainly arthrotropic velocity.

The usual high incidence of elective localization and marked lesions in joints was noted in this new series of experiments as in all series previously studied in which cultures were made from patients with arthritis. Thus, in 64 per cent of one hundred and six rabbits that were given injections of sixty-four strains isolated from patients with arthritis, arthritis developed, in 21 per cent lesions developed in the muscles in 8 per cent in the endocardium and in 6 per cent in the myocardium. Lesions of nerves did not develop in any. In 71 per cent of seven rabbits that were given injections of one or another of four strains

isolated from patients with "rheumatic" arthritis, arthritis developed, in 43 per cent, myositis developed, in 29 per cent, endocarditis, and in 29 per cent, myocarditis. In none did lesions of the nerves develop. In 37 per cent of thirty-five rabbits that were given injections of one or another of eight strains derived from persons suffering from neuro-myositis, arthritis developed in 66 per cent, myositis, in 11 per cent, endocarditis, in 11 per cent, myocarditis, and in 46 per cent, lesions of the nerves. These results are in sharp contrast with those following the injection of strains obtained in a similar manner from normal persons and from persons (control group) ill with diseases other than the arthritic group. In experiments with strains representing the control group, in only 21 per cent of eighty-seven rabbits that were given injections of one or another of forty-three strains did arthritis develop, in 8 per cent, myositis developed, in 3 per cent, endocarditis, in 6 per cent myocarditis and in 1 per cent lesions of the nerves. The lesions of the joints in the present series of experiments were usually more marked and more joints were involved as in former studies, in the animals receiving injections of organisms derived from patients with arthritis than in the animals which received injections of organisms from the control group. The power of the streptococcus obtained in cases of arthritis to produce arthritis was roughly proportional to the acuteness of the attack suffered by the patient from whom the organisms were isolated and to the number of streptococci that had arthritogenic velocity in the culture. As indicated, the strains obtained in the cases of "rheumatic" arthritis associated with involvement of the heart, in this series of experiments as in the former series, had, in addition to marked affinity for the joints marked affinity for the heart, especially for the heart valves and myocardium, whereas those isolated in cases of chronic infectious arthritis without involvement of the heart had marked affinity for joints and slight affinity for the heart. The cataphoretic velocity of the two groups of strains was about the same, although individual organisms having neurotropic velocity were more common in the cultures from the cases of rheumatic arthritis. There was little difference in the cataphoretic velocity and indeed in the localizing power of the streptococci as isolated from the various sites of infection in individual cases of arthritis, although it sometimes happened that the velocity of streptococci in cultures from one of several foci in an individual case was atypical. It was common in cases of neuromyositis, when more than one focus was cultured, that arthritogenic velocities predominated in one and neurotropic velocities in others.

In the strains from patients suffering from myositis, with or without arthritis, associated with a variable degree of neuritis, comprising the neuromyositis group, the affinity for joints, muscles and nerves

corresponded closely with the affected regions of the patients from whom the organisms were isolated, also, the organisms had chiefly the corresponding characteristic cataphoretic velocity or potential. The strains isolated from lesions in muscles of inoculated animals remote from nerves and from joints contained a preponderance of streptococci having arthrotropic velocity, and those isolated from the affected nerves remote from lesions in muscles had chiefly neurotropic velocity. However, nearly all of these cultures from lesions that were produced in animals contained a mixture of streptococci having chiefly arthrotropic and neurotropic velocities (fig 1), as did the strains isolated from atria of infection of patients. The results in one case of severe, incapacitating, acute neuromyositis, radiculitis and arthritis were especially striking. The cataphoretic velocity of the streptococcus as isolated on two occasions a week apart, from the nasopharynx and infected pockets surrounding teeth, was typical in all cultures tested. Of eight rabbits given intravenous injections, arthritis developed in seven, lesions of the muscles in seven, chiefly along nerves and blood vessels, and hemorrhagic lesions in nerves and nerve sheaths in seven. In addition to symptoms of pain in this patient there were marked nervousness and nervous exhaustion, which persisted for weeks, but following removal of the infected teeth there was gradual recovery. Concomitant with the marked involvement of the central nervous system, the streptococcus penetrated the central nervous system following intravenous inoculation of four rabbits, producing meningo-encephalitis and radiculitis.

Blood-agar platings of cultures from infected teeth of patients and of turbid fluid from affected joints of animals that had been given injections were nearly always sterile when cultures in dextrose-brain broth or in dextrose-brain agar revealed pure cultures of streptococci that grew in short chains, and that had chiefly arthrotropic velocity. Cultures of turbid fluid from the joints, even in dextrose-brain broth and dextrose-brain agar, sometimes remained sterile. Especially was this so in cultures from animals that had been given injections a considerable time previously. By the making of cultures from excised pieces of bone and other tissues, positive results were obtained more often, but even under these circumstances growth sometimes remained absent. Smears of fluid from the joints sometimes revealed undoubted diplococci when cultures remained sterile, and sometimes growth of streptococci occurred when no organisms could be found on direct examination of stained films. It occurred to me that perhaps the reaction in the joints might be due to a filtrable virus, or that the streptococcus might have become filtrable and difficult to grow. Accordingly, filtrates were made of emulsions of tissues of involved joints, of negative cultures of fluid from the joints in dextrose-brain broth, of negative cul-

tures of emulsions of tissue and of positive cultures of streptococci in this medium. All cultures from filtrates of tissues that had remained sterile, from filtrates of fluid from the joints and from sterile cultures of these remained sterile, whereas filtrates of some of the positive streptococcic cultures in dextrose-brain broth from areas of infection and from joints revealed pure cultures of streptococci having chiefly arthrotropic velocity and corresponding elective localizing power. Intravenous and intra-articular injection of negative cultures and filtrates negative on culture have never caused arthritis, whereas similar injection of corresponding filtrates of positive cultures have yielded mild "toxic" lesions. Cultures from joints showing these lesions were always sterile, and direct transfers of exudates thus obtained to joints of other rabbits failed to produce arthritis.

Staphylococci were frequently isolated, but nearly always in small numbers and never in pure cultures, from apexes of teeth and from the joints of rabbits that had been given intravenous injections of primary cultures in dextrose-brain broth, even in instances in which platings of the culture injected revealed colonies of staphylococci. Pure cultures of staphylococci, obtained only rarely in the primary culture in dextrose-brain broth, and those fished from single colonies of cultures from the various foci of infection and joints of animals that were given injections of cultures of streptococci in which a small number of staphylococci were present, nearly always revealed mixed velocity, and never a preponderance of organisms having arthrotropic velocity. The serum of patients with chronic infectious arthritis in no instance had a greater velocity-slowness effect on the staphylococci isolated than had normal serum, indicating that these staphylococci were not etiologic.<sup>15</sup>

As has been shown previously, freshly isolated cultures from areas of infection such as the nasopharynx of normal persons and of persons ill with diseases other than arthritis, sometimes produce arthritis in animals following intravenous injection, but the arthritis is usually mild in degree, and the incidence is far lower than that following injection of cultures from patients with arthritis. On the basis of studies of cataphoresis this should be so, for streptococci having arthrotropic velocity are uniformly present in considerable numbers in the nasopharynx of normal persons and sometimes of persons ill with diseases other than arthritis. The cataphoretic velocity of the streptococci obtained from the joints of animals in which arthritis had developed following injection of cultures derived from normal persons and from persons ill with diseases other than arthritis was chiefly arthrotropic.

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<sup>15</sup> Crowe, H. W. *Bacteriology and Surgery of Chronic Arthritis and Rheumatism with End-Results of Treatment*, New York, Oxford University Press, 1927.

In one group of normal persons, swabbings were repeatedly made before, during and after an epidemic of influenza, and marked variation in cataphoretic velocity of streptococci from the nasopharynx was noted with changes in season. The velocity of the streptococci cultured from the sets of swabbings made during the epidemic resembled that of the streptococci obtained in cases of influenza. In the cultures made from swabbings soon after the epidemic of influenza had disappeared, the velocity of the streptococci became markedly arthrotropic, and one person who had a particularly great preponderance of streptococci of arthrotropic velocity had an attack of arthritis shortly thereafter. Coincidental with this, and with a high incidence of arthrotropic velocity of streptococci in cultures from the nasopharynx as patients recovered from influenza, there was a noticeable increase in the number of cases of arthritis. The streptococcic strains from patients with influenza, after culture on blood-agar, acquired arthrotropic velocity and marked affinity for joints. Three months after the epidemic of influenza had disappeared, the cataphoretic velocity of the streptococci from the nasopharynx of the group of normal persons, swabbed repeatedly, had again become characteristic of the velocity of streptococci derived from normal persons in nonepidemic times. Details of these experiments will be published elsewhere.

In addition, considerable variation in the percentage incidence of streptococci having arthrotropic velocities has been found; the incidence sometimes approaching that obtained in cases of chronic infectious arthritis and in different groups of normal persons, particularly in groups swabbed in different localities and institutions at different seasons. Arthrotropic velocity and elective localizing power were particularly high in streptococci isolated from persons who had arthritis, and who were resident at an institution where an epidemic of acute arthritis was occurring; the epidemic was traced to a *Streptococcus lacticus* starter used in preparing cottage cheese from pasteurized milk. It might well be that the abnormally high incidence of arthritis in rabbits given injections of cultures from normal persons reported by Valentine and Van Meter<sup>9</sup> may have been due to incidental causes such as these. Moreover, cataphoretic studies have been of great value in explaining the reason for unusual localizations in certain instances, such as were noted by these investigators in their relatively small number of experiments and by me throughout many years of effort in work on elective localization. Most of these puzzling irregularities, considered by Valentine and Van Meter<sup>9</sup> as explainable by the law of chance, have been found to be due to sudden dissociation of strains as determined by cataphoresis. The changeability or mutability of streptococci is basic to the concept of elective localization, indeed, the theory had its origin in

the work on transmutation of pneumococci and streptococci. The isolation of streptococci having chiefly arthrotropic velocity from various areas of infection in cases of arthritis in the absence of influenza has been almost constant over a period of several years, and on repeated occasions over a period of many months, in some cases of progressive chronic arthritis. Likewise the streptococci from areas of infection of persons having chronic encephalitis and allied diseases of the nervous system have been found to have chiefly neurotropic velocity. However, with the appearance of an epidemic of influenza, the streptococcic flora of the nasopharynx of normal persons generally within the epidemic zone, and of persons suffering from arthritis, encephalitis and other diseases became influenzal, and, most remarkable of all the respective characteristic streptococci isolated in nonepidemic times with great regularity from the apexes of pulpless teeth of persons having arthritis or encephalitis and other diseases became influenzal irrespective as to whether the patients had had influenza or not. This peculiar condition of the streptococcus from teeth persisted for several months and disappeared as the streptococcic flora of the nasopharynx again became normal in normal persons, and characteristic of the disease in question in patients presumably suffering from disease due to streptococci.

Drs R. L. Cecil, E. E. Nicholls and W. J. Stansby<sup>12</sup> have given me the opportunity of studying three of their typical strains of streptococci isolated from the blood in cases of chronic infectious arthritis. All produced marked hemolysis on blood-agar plates and all grew well in dextrose-brain broth, but produced a slightly granular growth instead of a diffuse growth as do the strains of streptococci which I isolate. However, most of the streptococci in cultures in dextrose-brain broth and on blood-agar plates had arthrotropic velocity through a series of rapidly transferred cultures. All produced marked arthritis in rabbits following intravenous injection in a dosage like that used with my strains, and from the joints pure cultures of hemolytic streptococci were isolated. The streptococci in the cultures from all but one joint had mainly arthrotropic velocity, whereas those of one joint had acquired a velocity closely resembling that of the streptococci derived from patients with influenza. This culture was injected intraperitoneally into two rats, both of which died with characteristic lesions of the pancreas, lung and pleura, and the strain isolated from the pleural exudate had influenzal velocity. These experiments were done at the time of an epidemic of influenza in Rochester. A similar dissociation of some of my strains, isolated in cases of arthritis, occurred in rabbits that had received injections during the epidemic of influenza, but such dissociation never occurred in the course of many similar experiments during the absence of epidemic influenza.



## COMMENT

The distribution of the different velocities of streptococci as isolated from atria of infection and from the stools of normal persons in which arthrotropic velocity is dominant seems to be a "resting phase" of streptococci, for the different strains having characteristic velocity, as isolated in studies of various diseases, tend, in nonepidemic times, to take on this distribution during prolonged cultivation on artificial mediums. Velocity of this distribution is displayed by streptococci on isolation from the nasopharynx of persons ill with diseases due to causes other than streptococci such as tuberculosis of the joints, and on isolation from the stools of normal persons and of patients with diseases not apparently due to streptococci (fig 1). This is likewise true of streptococci isolated in nonepidemic times from the milk of cows and from other dairy products. This distribution of different velocities is considered of basic importance, for it suggests, perhaps, that the great frequency of arthritis may be due in part to this cause.

During an epidemic of influenza, in addition to persons ill with influenza, a large proportion of normal persons and those ill with other diseases, such as arthritis and encephalitis, became carriers of the streptococcus having influenzal velocity. Following the epidemic, however, the streptococcal flora in each group again became characteristic. That of normal persons became normal, that of persons with arthritis became arthrotropic and that of persons with encephalitis became neurotropic. These and other facts indicate that dissociation or mutation of streptococci plays an important part in the etiology of various forms of arthritis and allied conditions, and of epidemic disease generally.

It has been shown in this and previous studies that persons having different diseases, for example chronic arthritis, are more or less permanent carriers of streptococci characteristic of arthritis, in that the streptococci possess an abnormally high elective affinity for joints, and in that a great preponderance have arthrotropic velocity. The fluids from the tissues of the patients seem to afford conditions favorable for streptococci to acquire these particular properties. On the basis of these observations, as I have previously suggested, it would seem that the inherited tendency to arthritis, or "rheumatic" diathesis, mentioned by the older writers, is more than the inheritance of weak joints, as is usually assumed. There is an inheritance of weak joints, plus, perhaps, a peculiar constitution or chemical make-up, which is favorable for streptococci present normally in atria of infection, or during epidemics of influenza, to acquire a peculiar arthrotropic cataphoretic velocity and infecting power.

## CONCLUSIONS

Streptococci isolated from patients who have arthritis, in the absence of epidemic influenza, have a characteristic arthritropic cataphoretic velocity and at the same time an elective localizing power, irrespective of whether the organisms are green-producing, indifferent or hemolytic on blood-agar.

The serum of patients having various forms of arthritis has specific cataphoretic velocity-slowng effects on the streptococcus isolated in cases of arthritis, and that is shown to have arthritropic velocity. An arthritropic cataphoretic velocity of the streptococcus as isolated and a specific slowing effect of the patients' serum on arthritropic streptococci have been found to be almost constant phenomena. The method of determining cataphoretic velocity has yielded results of etiologic importance, and has proved of great value in the control of the specificity and dosage of autogenous and heterologous streptococcus vaccines used in treatment. If this method is properly applied, it is no longer necessary to inject cultures from areas of infection intravenously into animals and to make cultures from their joints in order to be certain that the streptococcus isolated is etiologic or has characteristic infecting and antigenic power. Determination of the cataphoretic velocity usually suffices.

# BRONCHIAL DISINFECTION AND IMMUNIZATION

## I THE EFFECTS IN RABBITS OF INTRABRONCHIAL INJECTIONS OF VARIOUS CHEMICAL DISINFECTANTS

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The frequency of the chronic intractable bronchitides, extensive bronchiectasia and other nontuberculous suppurative infections of the bronchi and lungs commonly grouped under the designation of suppurative pneumonitis, along with the well established fact that ordinary medicinal treatment possesses little or no real value, renders this relatively large group of pulmonary infections worthy of further investigation in relation to both etiology and treatment. This is particularly true since bronchiectasis not unfrequently begins in childhood and sometimes results in semi-invalidism for many years and indeed for the balance of life.

Fortunately, bronchoscopic drainage and bronchial lavage have definitely improved the treatment and prognosis of bronchiectasis and these allied conditions. Bronchoscopic drainage, as developed by the brilliant investigations of Jackson, Tucker, Cleif and others, has at least largely aided in the treatment in those cases due to foreign bodies<sup>1</sup> and, along with bronchography, has greatly improved methods of diagnosis as well as provided a means for removing collections of purulent secretions and making direct or topical applications of medicinal agents. Unfortunately, however, the bronchoscope cannot reach the smaller bronchi, and it may not be practical to make direct applications of bactericidal agents through it with the frequency that is demanded. For these reasons the possibilities of bronchial lavage as developed by Stitt<sup>2</sup> and others, as well as the intubation method recently described by Iglaue<sup>3</sup> for the introduction of iodized oil for bronchography in chil-

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1 Jackson, C. Suppurative Diseases of the Lung Due to Inspired Foreign Body Contrasted with Those of Other Etiology, Surg, Gynec & Obst **42** 305, 1926

2 Stitt, H. L. Bronchial Aspiration and Irrigation with a Hypertonic Saline Solution, J Med **8** 112, 1927

3 Iglaue, S. Advantages of Intubation Method of Introducing Iodized Oil for Bronchography in Children, J A M A **97** 1517 (Nov 21) 1931

dien, commands considerable interest. In other words, any method that permits the frequent, even the daily removal of bronchial secretions and the instillation of bactericidal and bacteriostatic agents with the minimum of discomfort and danger is to be welcomed as opening up a possible means for improving the treatment of these distressing infections.

Certainly the ease and success attending bronchography in adults and children with instillations of iodized oil indicate that the pulmonary tissues may tolerate relatively large amounts of bland solutions capable of reaching the infected finer divisions of the bronchi beyond the reach of direct applications through the bronchoscope, hence, the possibility of improving the treatment of bronchiectasis and allied conditions by the local application of chemotherapeutic substances as well as with such biologic agents as vaccines, bacteriophages and antiviruses is established.

#### ETIOLOGY

While it is not within the scope of this communication to discuss in detail prevailing views and personal investigations bearing on the etiology of the intractable bronchitides and bronchiectasia, a brief reference to the subject is necessary in relation to these studies undertaken in regard to intrabronchial disinfection and immunization.

Aside from those cases due to probable congenital deficiencies in the bronchi and foreign bodies, it is my opinion that the majority are due to bacterial infection and especially to streptococci and staphylococci. At least this is the impression gained during the past six years as the result of bacteriologic examinations of a large number of specimens collected by bronchoscopy and submitted for examination by Dr. Chevalier Jackson and Dr. Gabriel Tucker.

In my experience, streptococcic infections are by all odds the most frequent and important and appear to be the prevailing infection in both early and late cases of purulent bronchitis and bronchiectasis. Indeed, they have not infrequently been present in pure cultures, and considering the fact that they have been collected under conditions greatly minimizing or entirely removing the chances of contamination with saliva with reasonable certainty, I have the conviction at present that they bear an important etiologic relationship to these infections. Staphylococci, pneumococci, various gram-negative diplococci, including *M. catarrhalis*, diphtheroid bacilli, *B. pyocyaneus* and *B. Friedlander*, are also encountered in chronic infections as would be expected, but streptococci, staphylococci and pneumococci would appear to be the more important in relation to the primary infection.

Spirochetes are sometimes seen in direct smears and more especially by dark-field examination, but not in my experience with the

frequency suggested by Smith<sup>4</sup> and others. In view of the numerous species to be found in the saliva and gingival secretions, especially in adults, it is to be expected that they may reach the bronchi in chronic infections and constitute secondary infection. However, it is possible, in some cases at least, that they may possess the etiologic importance assigned to them by Smith in producing primary infection of the bronchial walls and favoring the development of pockets analogous to the rôle of *Spirochaeta pallida* in the production of aneurysms, but I hesitate accepting this view in individual cases unless relatively large numbers are found in the secretions or until microscopic examination of tissues removed at autopsy more definitely establish this relationship. Furthermore, it would appear that *Spirochaeta vincentii* and *B. fusiformis* may produce a type of Vincent's infection of the pulmonary tissues, but in the large majority of the chronic bronchitides and bronchiectasia my findings assign a more frequent and important rôle to the bacteria with special reference to the streptococci.

Various molds and yeasts are sometimes recovered in cultures of secretions from chronic bronchial infections, but so far these have been almost entirely of the various *Aspergilli* and *Penicillia* commonly found in the dusts of the house and factory. It is to be expected that molds of these and other species may have some bearing on the production of allergic asthma, but with the exception of such pathogenic species as *Actinomyces* their rôle and importance as etiologic agents in suppurative pneumonitis are as yet to be determined.

#### PRINCIPLES OF CHEMOTHERAPY APPLIED TO BRONCHIAL DISINFECTION

While sanatorium regimen, frequent postural drainage, elimination of mouth and sinus infection, bronchoscopic removal of foreign bodies and secretions and various surgical procedures are logical measures of value in the treatment of suppurative pneumonitis, as recently emphasized by Alexander and Buckingham,<sup>5</sup> yet it would appear that the possibilities of local disinfection by chemotherapeutic agents, applied bronchoscopy or bronchial lavage are worthy of serious attention.

However, but little has been done so far in this direction. Castex, Heidenreich and Repetto<sup>6</sup> have reported favorably on intrabronchial

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4 Smith, D. T. Relation of Vincent's Angina to Fusospirochetal Disease of the Lungs, *J. A. M. A.* **94** 23 (Jan. 4) 1930. Gives a good review of earlier literature.

5 Alexander, J., and Buckingham, W. W. Treatment of Nontuberculous Suppurative Pneumonitis, Abscess and Bronchiectasis, *J. A. M. A.* **95** 1478 (Nov. 15) 1930.

6 Castex, M. R., Heidenreich, A. J., and Repetto, R. L. Le salvarsan par voie trachéale dans le traitement des Processus fétides de l'appareil respiratoire, *Bull. Acad. de méd., Paris* **95** 131 (Feb. 9) 1926.

injections of neoarsphenamine in the treatment of spirochetic infections, and Stiehm,<sup>7</sup> the Ballons<sup>8</sup> and others refer to the possible curative effects of intrabronchial injections of iodized poppy seed oil 40 per cent although the bactericidal activity of the latter is so low that it is possible that the benefit observed was due to other factors. Gomenol has been applied by Jackson, Tucker and others through the bronchoscope with apparently some benefit, which is to be expected, since this oil possesses some bactericidal activity, as I shall discuss later, but otherwise no systematic attempts at local disinfection appear to have been made although a number of antiseptics have been tried.

Naturally a relatively large list of bactericidal agents is available for the choice of compounds to be employed, but it would appear that substances selected for attempted bronchial disinfection should possess the following essential properties:

1 A reasonably high degree of parasiticidal activity in the presence of pus and especially for streptococci, staphylococci and other bacteria, spirochetes and fungi

2 Be rapidly parasiticidal because the time of contact must be necessarily brief

3 Preferably stain the tissues in order to prolong antiseptic or bacteriostatic action

4 Possess the maximum degree of penetrability in order to reach and destroy micro-organisms entrenched in cells and tissues

5 Be free of injurious effects on phagocytes in order not to interfere with phagocytosis which doubtless exerts an important rôle in the mechanism of resistance and recovery

6 Be free of injurious effects on the pulmonary tissues. That is, the chosen antiseptic should not exert excessive hyperemia or inflammatory changes, abolish the cough reflex or interfere with ciliary action and bronchial peristalsis

7 Be sufficiently low in toxicity to spare the kidneys, liver and other organs injurious effects following absorption from the lungs

8 Furthermore, the solution employed for irrigating the bronchi and for preparing solutions of the chosen antiseptic should not favor the development of edema, especially since the tissues are already injured by infection. For this reason the use of calcium and potassium salts with sodium chloride in any irrigating fluid is regarded as superior to sodium chloride alone, and the following Martin-Bledsoe irrigant has been recommended:

	Gm or Cc
Sodium chloride	10  5
Potassium chloride	0  42
Calcium chloride	0  84
Distilled water	1,000  0

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7 Stiehm, R. H. Treatment of Bronchiectasis with Lipoidol with Report of Nineteen Cases, *Wisconsin M. J.* **29** 556, 1930

8 Ballon, R. H., and Ballon, H. C. The Value of Bronchoscopic Injections of Lipoidol in the Diagnosis and Treatment of Bronchiectasis, *J. Laryng. & Otol.* **44** 153, 1929

Stitt finds it convenient to have this solution ready in concentrated form as follows

	Gm or Cc
Sodium chloride	263  7
Potassium chloride	10  6
Calcium chloride (desiccated)	21  0
Distilled water	1,000  0

For use, 20 cc of this solution is diluted to 500 cc with distilled or boiled water

The solution contains, therefore, the three salts originally advocated by Ringer for maintaining the physiologic activity of surviving tissue and may be regarded as a physiologically balanced mixture. The concentration of sodium chloride has been raised somewhat above the point where it will prevent the swelling of injured cells, while the concentration of calcium chloride is several times higher to maintain the dehydrating effects of the salts as long as possible.

Since the exudates in suppurative pneumonitis are usually plastic and so rich in coagulating principles as to coagulate solid or almost so in the Tucker, Clerf or other collectors employed in bronchoscopic drainage, it would appear advisable to employ a fluid possessing liquefying or digestive properties. For this reason the alkaline antiseptics like surgical solution of chlorinated soda (Dakin's solution), command special attention, but unfortunately some chemical antiseptics are precipitated by alkalis and the pulmonary tissues greatly irritated by concentrations sufficient for liquefaction of the exudates. It may be that proteolytic enzymes may be of service in this direction, but so far my associates and I have not been able to work out a satisfactory solution of them for irrigating purposes.

But even if the foregoing requirements are fulfilled, and I believe they may be by some antiseptics, as discussed later, the important problem of adequate application to the infected tissues must be solved. This refers not only to sufficiently wide distribution in the infected areas of the lungs along with adequate drainage of the secretions but also and more importantly to sufficient frequency of application.

Thus antiseptics may successfully reduce the number of pathogenic bacteria to some extent and otherwise fulfil these essential requirements, but because the bacteria escaping destruction soon begin to multiply under the favorable conditions of the lungs the original state is soon restored unless a way and means for sufficiently frequent applications is worked out.

In other words, it would appear that but little benefit may result from an occasional application of a bactericidal agent for example once a week by bronchoscopic application or lavage. It would be necessary to work out a method whereby applications may be made at

more frequent intervals, even daily, for a while at least, with the minimum of discomfort and expense to the patient. For this reason I am very much interested in the possibilities of bronchial lavage, especially because it may not only afford a means of removing and washing out the purulent secretions but provide a method of instilling relatively large amounts of bacteriostatic or bactericidal solutions for reaching areas beyond direct application through the bronchoscope. In other words, it would appear that but little is to be expected from the application of antiseptics on gauze pads through the bronchoscope, because but small areas can be reached and the time of contact with the infected tissues is too brief, whereas, if it were possible to introduce and leave relatively large amounts of antiseptic solution at frequent intervals, a wider distribution and more prolonged contact may be secured with possibly greater therapeutic benefit, providing the procedure was found entirely safe and feasible.

Of course, the intravenous or intramuscular injection of chemotherapeutic agents of curative value would be the ideal treatment but there is nothing of proved value to employ by these routes of administration except neoarsphenamine or bismarsen<sup>9</sup> for the treatment of Vincent's or other spirochetic infections of the lungs.

#### DANGERS AND CONTRAINDICATIONS TO BRONCHIAL DISINFECTION

No doubt certain dangers may attend attempts at bronchial disinfection by the direct application and instillation of antiseptics by bronchoscopy or bronchial lavage. It has already been shown by Stitt and others that 15 cc. of solution may be introduced with each inspiration. The cough reflex expels the solution along with the thickropy secretions, so that as much as 250 cc. may be used for cleansing purposes. Under these conditions at least some of the antiseptic remains for a while in contact with the infected tissues, but my main idea was to determine if it is possible and safe to leave a portion of the last instillation for more prolonged bactericidal and bacteriostatic action without local and general injury.

The question of spreading the infection to healthy portions of the lung is important in this connection, but if bactericidal solutions are employed it would appear that this possible or theoretical danger is greatly minimized. Likewise, the danger of forcing or permitting the antiseptic solution to reach the terminal alveoli with the production of infection and pneumonitis is of importance, but I believe that it is possible to determine this danger by suitable experiments on rabbits.

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<sup>9</sup> Kolmer, J. A. Bismuth Arsphenamine Sulphonate (Bismarsen) in the Treatment of Syphilis and of Other Spirochetic Infections, *Arch. Dermat. & Syph.* 21: 394 (March) 1930.



Advanced cardiovascular disease, pulmonary malignant conditions and pulmonary tuberculosis may be accepted as contraindications, but it is not unreasonable to hope and expect that these methods may find a safe and useful field of application in the treatment in some cases of the latter if the results of suitable experiments on the lower animals shows that bronchial lavage and instillation of carefully selected bactericidal agents is a safe procedure

#### PURPOSE OF INVESTIGATION

With these considerations in mind, the main purpose of this investigation was to select a number of the more promising bactericidal agents most nearly meeting the requirements for bronchial disinfection as outlined and determine the tolerance of the lungs of rabbits for them by repeated intrabronchial injection

For these purposes a large number of chemical agents were tested for rapidity of bactericidal activity in the presence of protein and a number of them injected intratracheally into rabbits every two or three days in doses as high as 1 cc per kilogram of weight of dilutions proving completely bactericidal *in vitro* in five minutes or less

After from six to twenty-four instillations under ether anesthesia, the trachea, lungs and kidneys of each animal were examined macroscopically and microscopically to determine the degree of toxicity and tolerance of the tissues for each antiseptic with special reference to the bronchi. In this manner I hoped to determine whether or not it is safe not only to irrigate the lungs with bactericidal solutions but more importantly to leave relatively large amounts in the lungs without producing irritation or inflammation of the tissues. I also hoped to determine whether or not the absorption of the antiseptic from the lungs produced evidences of general toxicity with special reference to possible injury of the kidneys

#### BACTERICIDAL ACTIVITY OF VARIOUS CHEMICAL AGENTS IN RELATION TO BRONCHIAL DISINFECTION

The preliminary bactericidal tests were conducted with a strain of hemolytic streptococcus and *Staphylococcus aureus*. While the value of these tests is limited, by conducting them in a medium rich in protein at body temperature the results are not without significance in the selection of compounds for intrabronchial disinfection

The technic employed was simple, as follows. 1 To 90 cc of sterile ascitic fluid was added 10 cc of a twenty-four hour broth culture of the test organism, and amounts of 2 cc were placed in sterile test tubes. 2 Solutions of each chemical compound were prepared in physiologic solution of sodium chloride and varying dilutions added in

amounts of 2 cc each. Under these conditions the bactericidal action of each compound was determined for relatively large numbers of the organisms in a 50 per cent dilution of ascitic fluid representing a large amount of protein approximating the conditions of inflammatory exudates. 3 These mixtures were kept in a water bath at 37 C and subcultured at the end of five minutes in order to select substances on the basis of fairly rapid bactericidal action.

The substances tested and the approximately highest dilutions completely bactericidal for the two organisms at the end of five minutes are shown in table 1.

As expected practically all of the substances tested were more bactericidal for the streptococcus than for the staphylococcus, which is

TABLE 1—*Bactericidal Tests*

Compound	Highest Bactericidal Dilution in Five Minutes	
	For Streptococcus Haemolyticus	For Staphylococcus Aureus
Gentian violet	1 6,000	1 4,000
Acriflavine base	1 6,000	1 3,000
Equal parts of gentian violet and acriflavine	1 6,000	1 4,000
Rivanol*	1 3,000	1 1,500
Merodicein*	1 10,000	1 5,000
Mercurochrome	1 200	1 100
Mercurophen*	1 20,000	1 15,000
Metaphen	1 60,000	1 30,000
S. T. 37 (1 1,000 hexylresorcinol)	1 3	1 2
Potassium permanganate	1 175	1 75
Mild silver protein	1 100	1 20
Gomenol*	1 60	1 8
1% iodine in 25% alcohol	1 75	1 75
Surgical solution of chlorinated soda	1 30	1 4
Chloramine T	1 600	1 400
Dichloramine T	1 300	1 75
Iodized oil	None	None
Neocarsphenamine	1 50	1 30

\* Merodicein (mono hydroxy mercuri di iodo resorcin sulphonphthalein), mercurophen (sodium oxymercury orthomtrophenolate), rivanol (a flavine dye) and gomenol (a preparation similar to oil of eucalypt) are proprietaries and have not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

fortunate in view of the fact that the former predominate in the secretions of purulent bronchitis and bronchiectasis.

Merodicein is of special interest, not only because it is a new compound possessing bactericidal activity but because it is a dye substance resembling mercurochrome-220 soluble in appearance, freely soluble in water and without precipitating effects on proteins and albumins. It is the disodium salt of mono-hydroxy-mercuri-di-iodo-resorcin-sulphonphthalein containing 22.78 per cent mercury, synthesized by Dunning and Farinholt.<sup>10</sup> Drake and Dunning<sup>11</sup> found it capable of killing

10 Dunning, F., and Farinholt, L. H. J. Am. Chem. Soc. **51**: 804, 1929.

11 Drake, W. E., and Dunning, F. Organic Antiseptics. Bacteriologic Study of a New Series, J. Infect. Dis. **48**: 366 (April) 1931.

*B. typhosus* in a dilution of about 1 : 22,500 in five minutes and *Staphylococcus aureus* in about 1 : 2,000. In our tests its bactericidal activity was much less because we employed large numbers of organisms and a menstruum of 50 per cent ascitic fluid representing a large amount of protein, which always reduces bactericidal activity *in vitro*. Macht and Cook<sup>12</sup> have reported that doses of from 0.010 to 0.020 Gm per kilogram of weight by intravenous injection were generally well borne by rabbits, with but slight effect on the kidneys.

However, an objection to meriodicein as a bronchial irrigant is its toxicity, evidently due in a large part to the content of mercury. The same is true of mercurochrome which was bactericidal in our tests in about a 1 per cent solution (1 : 100), although this compound is about half as toxic. Mercurophen and metaphen are at least five or six times more toxic but were likewise from ten to twenty times more bactericidal and therefore may be used for bronchial irrigation in dilutions of 1 : 5,000 or higher.

The dyes, gentian violet, acriflavine and rivanol, were bactericidal in dilutions of about 1 : 4,000, and in view of their low toxicity command great interest in relation to bronchial irrigation, particularly solutions of equal parts of gentian violet and acriflavine, since the former is especially bactericidal for gram-positive organisms, including streptococci and staphylococci, while the latter is especially bactericidal for gram-negative organisms.

While S. T. 37, or 1 : 1,000 solution of hexylresorcinol, is likewise of interest in relation to bronchial disinfection because of its low toxicity, it is unfortunately rather low in bactericidal activity and required the use of an undiluted solution (1 : 1,000), or a 1 : 2 dilution.

Mild silver protein proved of considerable interest, not only in relation to its low toxicity and staining properties but because it proved bactericidal in solutions of from 5 to 10 per cent.

Potassium permanganate was bactericidal in dilutions of from 1 : 50 to 1 : 100, and therefore commands interest as an irrigant. Iodine in the form of a 1 per cent solution in 25 per cent alcohol was especially interesting because it proved bactericidal in dilutions as high as 1 : 50 of this stock 1 per cent solution. This and its low toxicity combined with staining and penetrative properties render iodine of special interest in relation to bronchial disinfection by irrigation. Iodized oil, however, proved entirely lacking in bactericidal activity, so that whatever therapeutic properties it has been found to possess in suppurative pneumonitis must be largely due to its high specific gravity in displacing purulent secretions and promoting their expectoration.

12 Macht, D. I., and Cook, H. M. Pharmacology and Toxicology of Monohydroxy-Mercury-Di-Iodo-Resorcin-Sulphonphthalein, *J. Pharmacol. & Exper. Therap.* **43** 571, 1931.

It will be noted that gomenol, which is widely used in bronchoscopy and for irrigation of the urinary bladder, was bactericidal in dilutions of from 1 5 to 1 20, and therefore of interest in relation to bronchial disinfection.

Considerable interest attaches to surgical solution of chlorinated soda because of its dissolving effects on purulent exudates, but unfortunately it is low in bactericidal activity, dichloramine T was more bactericidal while chloramine T was bactericidal in final dilutions as high as from 1 400 to 1 600 and therefore of considerable interest in relation to bronchial disinfection, although unfortunately rather irritating to the trachea and bronchi, as discussed later.

#### SPIROCHETICIDAL ACTIVITY OF VARIOUS CHEMICAL AGENTS IN RELATION TO BRONCHIAL DISINFECTION

Since spirochetes are not infrequently found in the exudates of chronic bronchitis, bronchiectasis and other types of suppurative pneumonitis, it is pertinent to inquire into the spirocheticidal activity of at least some of the bactericidal agents listed in table 1 in relation to bronchial disinfection, even though the exact etiologic status of these organisms is as yet unsettled except in some instances of pulmonary spirochetosis where such enormous numbers of spirochetes are found in the profuse exudates as to leave little or no doubt of their etiologic significance.

As shown in table 1, neoarsphenamine was completely bactericidal for *Streptococcus haemolyticus* and *Staphylococcus aureus* in dilutions of about 1 50. Mixtures of equal parts of 1 25 solution and bronchial secretions containing large numbers of various spirochetes (final dilution 1 50) showed complete loss of motility within five minutes, as determined by dark-field examination. Of course, this does not necessarily imply the death of the organisms, but it is likely that under the conditions the majority at least were crippled and probably destroyed.

Additional tests with other chemical agents are shown in table 2. As a general rule, the finer spirochetes (presumably *Sp. microdentium*) were more easily destroyed than the larger and coarser ones like *Sp. macrodentium*. It was surprising, however, that the final concentrations of various agents required to cause complete loss of motility of spirochetes in purulent secretions within five minutes were many times greater than required for bactericidal activity by the method employed. For example, gentian violet, acriflavine and rivanol were spirocheticidal in from 1 100 to 1 300 but bactericidal in from 1 3,000 to 1 6,000, merodicein was bactericidal in from 1 5,000 to 1 10,000 but spirocheticidal in only 1 25, mercurophen and metaphen were bactericidal in from 1 15,000 to 1 60,000 but spirocheticidal in only 1 1,000.

Numerous experiments by Akatsu<sup>13</sup> have shown that neoarsphenamine and other chemical compounds are more spirocheticidal for cultures of various spirochetes than for these organisms in the secretions. For example, neoarsphenamine was spirocheticidal in vitro for cultures of *Spirochaeta pallida* in 1:2,500, mercuric chloride, 1:10,000, and iodine in compound solution, 1:75. Apparently, however, the presence of pus and cells in purulent secretions greatly reduce spirocheticidal activity in vitro.

But these and numerous other experiments summarized by me<sup>14</sup> have shown that neoarsphenamine and probably other bactericidal agents possess well defined spirocheticidal properties in vitro by local application, and it is expected that lavage of the lungs in the various types

TABLE 2—*Spirocheticidal Tests*

Compound	Approximate Concentration Sufficient to Cause Loss of Motility in Five Minutes
Gentian violet	1:100
Acriflavine base	1:300
Rivanol	1:300
Merodicein	1:25
Merurochrome	1:50
Merurophen	1:1,000
Metaphen	1:1,000
S. T. 37 (1:1,000 hexylresorcinol)	Undiluted
Potassium permanganate	1:25
Mild silver protein	1:10
Gomenol	1:10
1% Iodine in 25% alcohol	1:5
Chloramine T in water	1:5
Neoarsphenamine	1:50

of suppurative pneumonitis with bactericidal solutions will likewise result in the destruction of at least some of those spirochetes with which the solutions come in direct contact.

#### TOXICITY OF VARIOUS CHEMICAL COMPOUNDS FOR RABBITS GIVEN BY INTRABRONCHIAL INJECTION

On the completion of these bactericidal and spirocheticidal tests, I now approached the more important part of the study in relation to bronchial disinfection, namely, the toxicity of the various agents employed for rabbits when given intratracheal injections.

13 Akatsu, S. The Resistance of Spirochetes to the Action of Hexamethylenetetramine Derivatives and Mercurial and Arsenic Compounds, *J. Exper. Med.* **25**: 363, 1917.

14 Kolmer, J. A. Principles and Practice of Chemotherapy with Special Reference to the Treatment of Syphilis, Philadelphia, W. B. Saunders Company, 1926, p. 342.

Preliminary experiments with iodized oil showed that the injection of 1 cc per kilogram of weight into the trachea resulted in a widespread distribution in the bronchi as determined by roentgen examination within a few minutes after the injection (fig 1) Sato<sup>15</sup> and the Ballons<sup>8</sup> found that injections of iodized oil into the lungs of the lower animals were well borne, and the results of our studies confirm these observations

Normal adult rabbits were employed, and under ether anesthesia solutions of the various compounds, in a dose corresponding to 1 cc per kilogram of weight, were injected directly into the trachea exposed by incision. As a general rule, the solutions of each compound corresponded approximately to those proving bactericidal for *Staphylococcus aureus* and *Streptococcus haemolyticus* in five minutes. It is true that the amount injected was large, since it corresponded to as much as

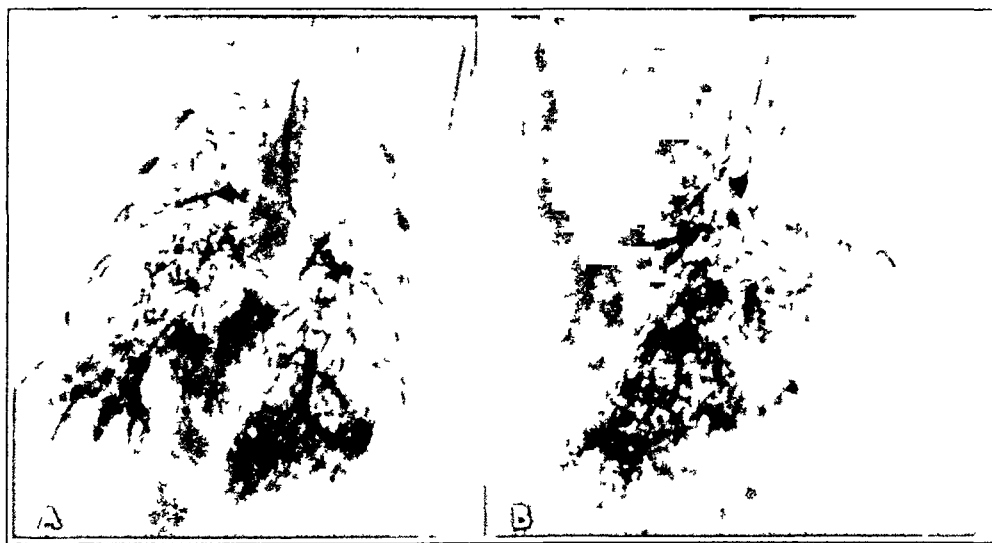


Fig 1—*A*, front view of the lungs of a rabbit, the roentgenogram was taken immediately after the intratracheal injection of iodized oil in dose of 1 cc per kilogram of weight. *B*, lateral view of the lungs of the same rabbit.

60 cc for an adult weighing approximately 135 pounds (61 Kg), but I purposely wished to make the tests reasonably severe, even though it was realized that if chemical disinfection were to be used in the treatment of human beings probably only 15 cc would be introduced at one time, followed by removal until about 250 cc had been used for lavage, and only from 5 to 15 cc would be left in the bronchi for more prolonged disinfection.

The injections were given every two days. As a general rule, several rabbits were employed for each solution and with many of the com-

15 Sato, T. Ueber den pathologisch-histologischen Einfluss des Lipoidols und die bakterizide Wirkung desselben, Mitt u allg Path u path Anat 5 183, 1929

pounds solutions were tried many times stronger than their bactericidal dilutions in order to intensify the toxic effects

On the death of the animals, or after from six to twenty-four injections had been given, autopsies were conducted with an inspection of the trachea, bronchi and lungs and sections were removed at different levels for histologic examination

TABLE 3—*Toxicity of Various Compounds for Rabbits by Intrapulmonary Injection*

Compounds	Dose, 1 Cc per kg of	Number of Injections	Results
Gentian violet	1 2,000	6	Survived
Acriflavine base	1 2,000	12	Survived
Equal parts of gentian violet and acriflavine	1 2,000	6	Survived
Equal parts of gentian violet and acriflavine	1 1,000	3 to 10	Died
Rivanol	1 2,000	12	Survived
Rivanol	1 1,000	10 to 17	Died
Merodicein	1 800	12	Survived
Mercurochrome	1 300	24	Survived
Mercurochrome	1 200	6 to 10	Died
Mercuraphen	1 5,000	12	Survived
Mercuraphen	1 1,000	5 to 7	Died
Metaphen	1 5,000	6 to 24	Survived
S T 37 (1 1,000 hexylresorcinol)	1 2	12	Survived
S T 37 (1 1,000 hexylresorcinol)	Undiluted	3 to 9	Died
Potassium permanganate	1 1,000	24	Survived
Potassium permanganate	1 500	3	Died
Mild silver protein	1 20	12	Survived
Gomenol	1 10	6	Survived
Gomenol	Undiluted	2	Died
1% iodine in 25% alcohol	1 25	12	Survived
1% iodine in 25% alcohol	Undiluted	3	Died
Surgical solution of chlorinated soda	Undiluted	6	Survived
Chloramine T in water	1 200	2	Died
Chloramine T in water	1 300	6	Survived
Dichloramine T in chlorcosane	1 20	2	Died
Dichloramine T in chlorcosane	1 200	6	Survived
Iodized oil	Undiluted	12	Survived
Neoarsphenamine	1 50	8	Survived
Martin Bledsoe saline (control)	Control	12	Survived
Paraffin, liquid petrolatum (control)	Control	12	Survived
Olive oil (control)	Control	12	Survived
Chlorcosane solution (control)	Control	12	Survived

Table 3 presents a summary of the results so far as survival of the animals is concerned. It shows the strength of the solutions employed, the number of injections in doses of 1 cc per kilogram every two days and whether the animals survived or succumbed. Variation in susceptibility of the animals to toxic effects was apparent, for example, three injections of a compound would sometimes result in the death of one animal, while a second would stand six injections and a third as many as twenty-four.

So far as the maximum tolerated doses of the various compounds employed are concerned, it would appear that the following represent the

approximate dilutions in doses of 1 cc per kilogram of weight every two days for from six to twenty-four injections

Gentian violet	1 2,000
Acriflavine base	1 2,000
Equal parts of these	1 2,000
Rivanol .	1 2,000
Merodicein	1 800
Mercurochrome	1 300
Mercurophen	1 5,000
Metaphen	1 5,000
S T 37 (1 1,000 hexylresorcinol)	1 2
Potassium permanganate	1 1,000
Mild silver protein	1 20
Gomenol	1 10
1 per cent iodine in 25 per cent alcohol	1 25
Surgical solution of chlorinated soda	Undiluted
Chloramine T in water	1 300
Dichloramine T in chlorcosane	1 200
Iodized oil	Undiluted
Neoarsphenamine	1 50

By reference to table 1, it is observed that these maximum tolerated dilutions were bactericidal for the streptococcus and staphylococcus, with the exception of S T 37, potassium permanganate and iodized oil. With several, however, the maximum tolerated dilutions were but slightly higher than the bactericidal dilutions, as in the case of the dyes (gentian violet, acriflavine and rivanol), mercurochrome, mild silver protein, gomenol, surgical solution of chlorinated soda, chloramine T, dichloramine T and neoarsphenamine, whereas merodicein, mercurophen, metaphen and the iodine solution were tolerated in dilutions from three to twelve times stronger than their bactericidal dilutions. From this standpoint the last mentioned would appear to be preferred for bronchial disinfection, but a final decision on the choice of compounds was based on gross and histologic examinations for possible evidences of pulmonary irritation.

#### PATHOLOGIC CHANGES PRODUCED BY INTRATRACHEAL INJECTIONS OF VARIOUS COMPOUNDS

I have determined with particular care the tolerance of the trachea, bronchi and lungs of rabbits for the various disinfectants employed in this study administered by intratracheal injection, and by means of macroscopic and microscopic examination of these tissues have sought to determine their irritating properties, since it is evident that any agent chosen for bronchial disinfection should be without any pronounced



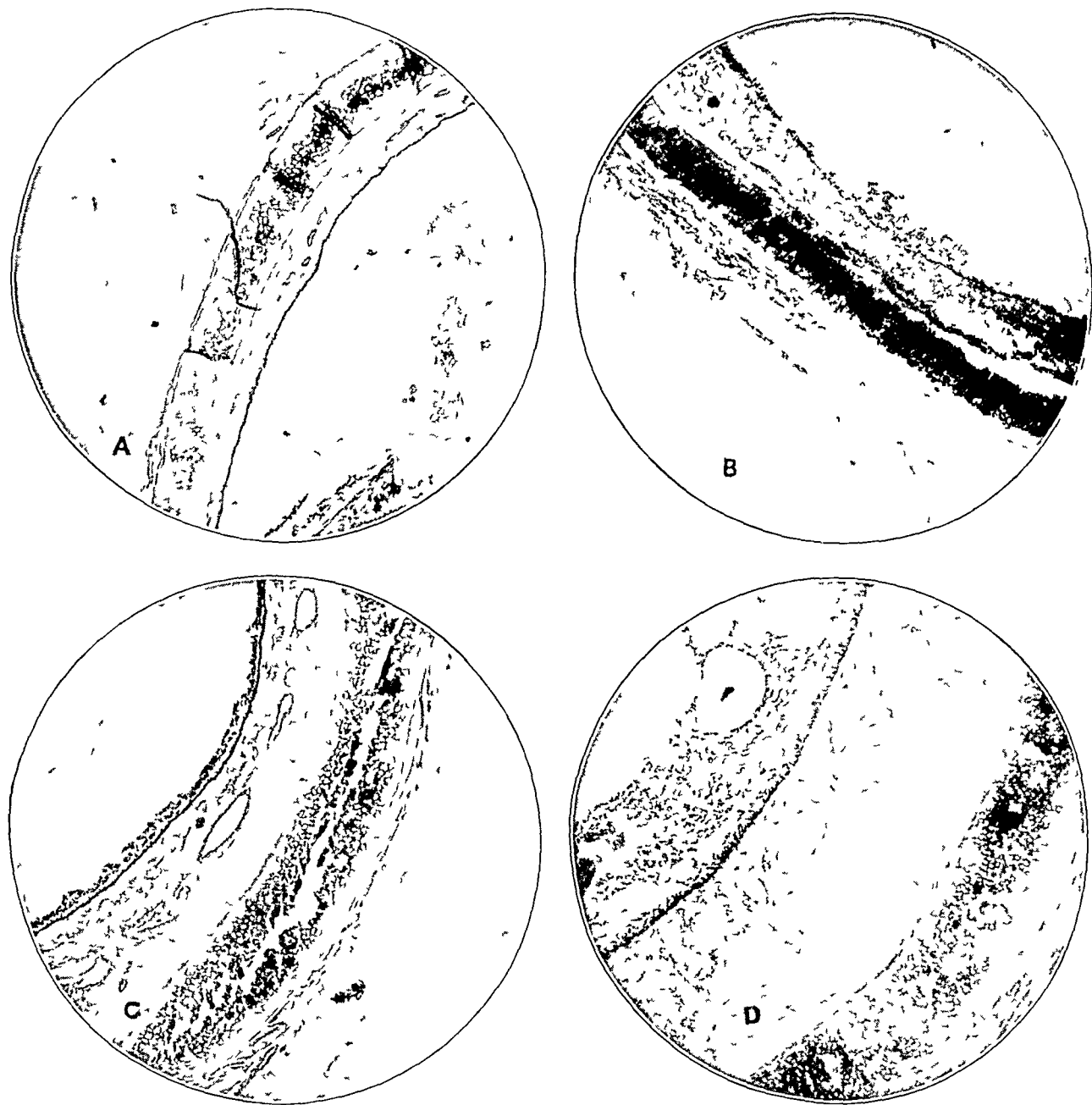


Fig 2—*A*, photomicrograph of a section of trachea. No changes were seen, the section was taken from the rabbit twenty-four hours after six intratracheal injections of 1:2,000 solution of acriflavine base in dose of 1 cc per kilogram. *B*, section of trachea showing congestion, edema and hemorrhagic extravasations in the submucosa with exfoliation of the mucosa, taken from a rabbit twenty-four hours after six intratracheal injections of 1:2,000 solution of gentian violet in dose of 1 cc per kilogram. *C*, section of trachea showing moderately severe tracheitis with extensive edema, taken from a rabbit twenty-four hours after four intratracheal injections of S T 37 (1:1,000) in dose of 1 cc per kilogram. *D*, section of trachea showing very severe tracheitis with extensive congestion, edema and leukocytic infiltration with inflammatory exudate on the mucosa, taken from a rabbit twenty-four hours after six intratracheal injections of dichloramine T in water (1:100) in dose of 1 cc per kilogram.

injurious effects At the same time sections of the kidneys of all animals were examined for evidences of renal injury as a measure of possible systemic toxic effects resulting from the absorption of the compounds from the lungs

For this purpose autopsies were conducted on all animals either immediately after death or twenty-four hours after the last intratracheal injection of solutions of each compound

At least from three to six rabbits were used for each compound, and the examinations conducted after intratracheal injection of from two to twenty-four doses of 1 cc per kilogram of weight

Sections from the trachea were made just above the bifurcation into the primary bronchi Sections of the lungs were selected from areas showing the maximum macroscopic changes, and sections were also made of both kidneys

Marked variations were observed in individual animals For example, an animal receiving three injections sometimes showed more pronounced histologic changes in the trachea, bronchi and lungs than a second animal receiving twelve injections of the same substance at the same time and in the same dosage Furthermore, the changes produced in the lungs were more or less localized rather than diffused, as a general rule the greater changes occurred in the right lungs, especially around the primary bronchus and in the lower rather than the upper lobes Sections were always taken from the most injured portions for histologic study

As would be expected, the various compounds employed produced different types and degrees of injury, but I do not consider the inclusion of a detailed description of the various injuries necessary to a complete understanding of this paper, hence, in order to be as brief as possible, I have summarized them in table 4

As expected, the bronchi have shown much more evidences of injury by all compounds than the trachea Indeed, with but few exceptions all of the compounds employed have produced some injury of the lungs, although in this connection it should be emphasized that the doses were large and amounted to 1 cc per kilogram every two days, corresponding to as much as from 60 to 70 cc for an adult human being of average weight Furthermore, it is to be remembered that all was left in the lungs after each injection rather than only a small portion But I have purposely made the conditions very severe in order to elicit the maximum of injury

With few exceptions all of the compounds were well borne by the trachea although the majority produced irritation of the bronchi and

especially the smaller branches, this was particularly true in the case of those rabbits receiving from six to twenty-four injections at intervals of two days. As a general rule, these bronchial changes were of mild degree and largely in the nature of hyperemia with some edema of the submucosa, although in some instances bronchial exudates of fibrin and polymorphonuclear leukocytes were produced.

As expected, the predominant pulmonary changes were in the form of peribronchial areas of hyperemia, edema and slight leukocytic infiltra-

TABLE 4—*Summary of Pathologic Changes in Rabbits Produced by Various Compounds by Intrapulmonary Injection*

Compound	Dilution, 1 Cc per Kg	No of Doses	Trachea	Lungs	Kidneys
Gentian violet	1 1,000	3 to 10	— to ++	+ to +++	—*
Gentian violet	1 2,000	6 to 12	— to +	— to +	—
Acriflavine	1 1,000	6 to 12	— to +	— to +	—
Acriflavine	1 2,000	6 to 12	—	—	—
Rivanol	1 1,000	6 to 17	—	+ to ++	—
Rivanol	1 2,000	6 to 12	—	+ to ++	—
Merodicein	1 2,000	6 to 12	—	— to +	—
Mercurochrome	1 200	6 to 24	—	— to +++	— to +
Mercurphen	1 5,000	6 to 12	—	—	—
Metaphen	1 5,000	6 to 24	—	— to ++	—
S T 37 (1 1,000 hexylresorcinol)	Undiluted	3 to 9	— to +++	— to +++	— to +++
S T 37 (1 1,000 hexylresorcinol)	1 2	6 to 12	—	— to +	—
Potassium permanganate	1 500	3 to 9	— to +	— to ++	—
Mild silver protein	1 20	3 to 11	—	— to +	—
Gomenol	1 10	4 to 12	—	— to +	—
1% Iodine in 25% alcohol	1 25	6 to 12	— to +	+ to +++	—
Surgical solution of chlorinated soda	Undiluted	3 to 8	—	+ to +++	++
Chloramine T in water	1 200	2 to 8	—	— to +	— to +
Dichloramine T in chlorcosane	1 100	2 to 8	+	+ to +++	+
Iodized oil	Undiluted	6 to 10	—	— to +	—
Neoarsphenamine	1 50	6 to 18	— to ++	— to +	— to +
Martin Bledsoe saline solution	Control	6 to 24	—	—	—
Liquid petrolatum	Control	6 to 10	—	— to +	—
Olive oil	Control	6	—	—	—
Chlorcosane solution	Control	6	—	—	—

\* The signs indicate the following: —, no demonstrable changes as applied to the trachea, (fig 2A) bronchi and lungs (fig 3A) or kidneys, +, slight congestion, edema and leukocytic infiltration as applied to the trachea (fig 2B) slight peribronchial infiltration, edema and hemorrhagic extravasations as applied to the lungs (fig 3B), acute congestion as applied to the kidneys, ++, moderately severe tracheitis with edema as applied to the trachea (fig 2C), acute diffuse hemorrhagic pneumonitis (fig 3C) as applied to the lungs, congestion and cloudy swelling as applied to the kidneys, +++ very severe tracheitis with extensive congestion, edema and leukocytic infiltration with inflammatory exudates (fig 2D) as applied to the trachea, severe suppurative bronchitis and pneumonitis with abscesses and liquefaction necrosis (fig 3D) as applied to the lungs, severe tubular or diffuse nephritis as applied to the kidneys.

tions of the alveoli. Indeed, practically all compounds produced such lesions, and especially in those animals receiving more than six injections at intervals of two days. In some instances, however, these changes were severe with relatively large areas of pneumonitis and multiple abscesses, as in the case of a large number of injections of mercurochrome, hexylresorcinol, iodine and chlorine compounds.

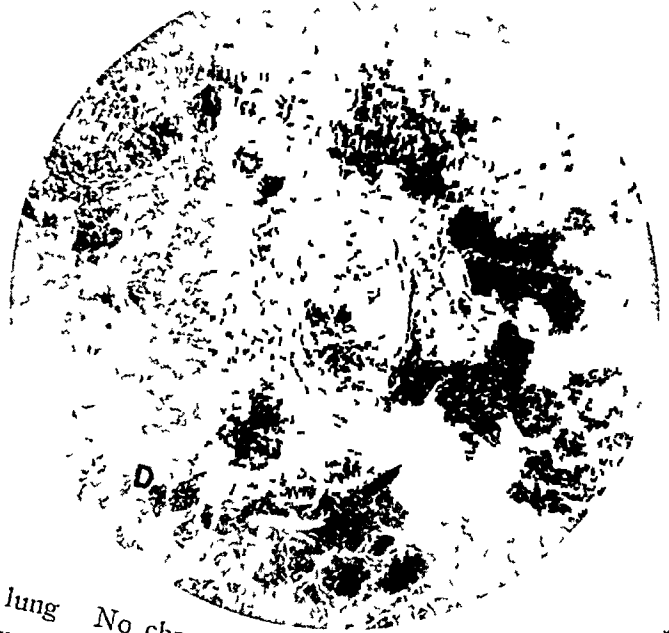
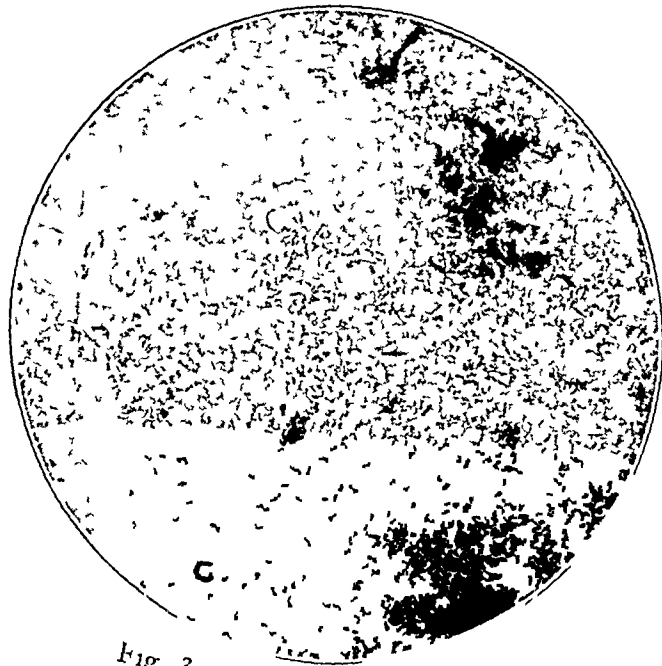
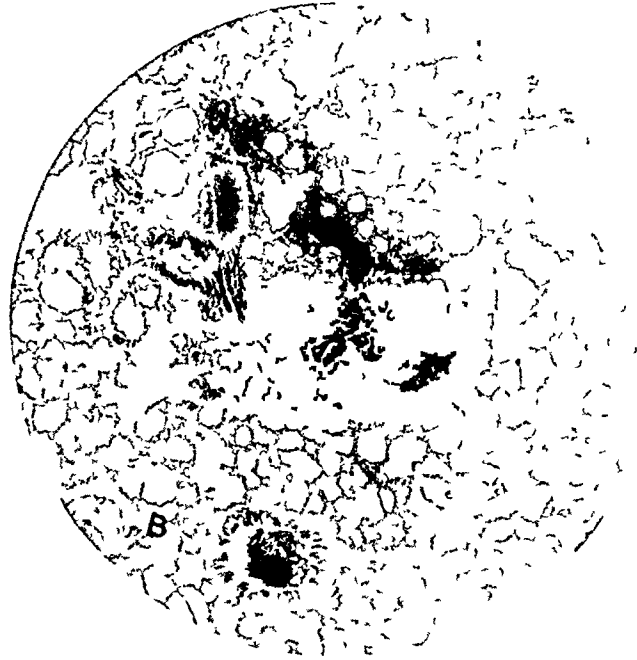
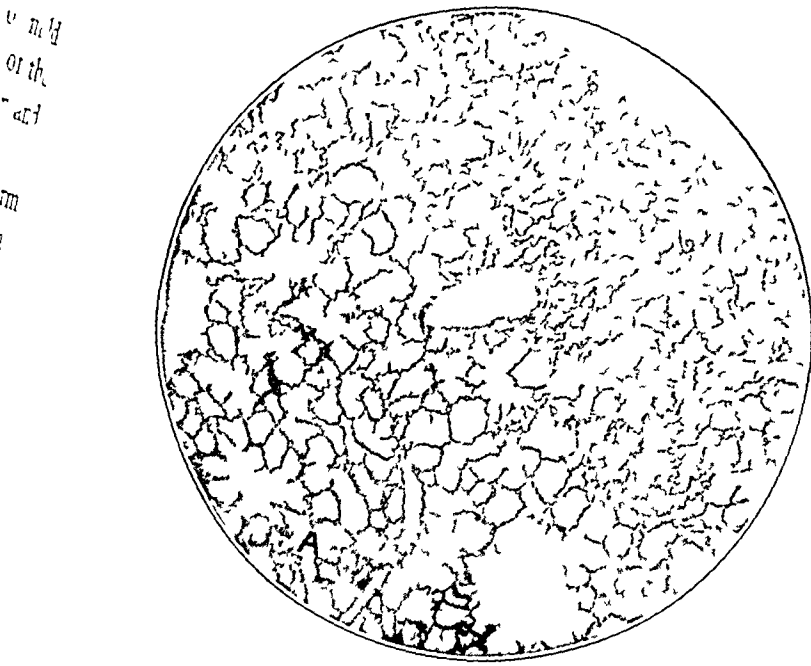


Fig 3—A, photomicrograph of a section of lung. No changes were seen, the section was taken from the lung of a rabbit twenty-four hours after four intratracheal injections of solution of acriflavine base 1 2,000 in dose of 1 cc per kilogram. B, section of lung showing hemorrhagic exudate in the bronchi with slight hemorrhagic and leukocytic infiltration of the peribronchial alveolar spaces, taken from the lung of a rabbit twenty-four hours after six intratracheal injections of a 1 2,000 solution of acriflavine in dose of 1 cc per kilogram. C, section of lung showing acute diffuse hemorrhagic pneumonitis, taken from the lung of a rabbit twenty-four hours after six intratracheal injections of a 1 1,000 solution of gentian violet in dose of 1 cc per kilogram. D, section of lung showing very severe suppurative pneumonitis with abscesses and liquefaction necrosis, taken from the lung of a rabbit twenty-four hours after four intratracheal injections of a 1 200 solution of mercurochrome in dose of 1 cc per kilogram.

As a general rule, there were no or but slight evidences of renal irritation, and such as were found occurred only among rabbits receiving six or more injections

However, I believe that it is entirely likely that lavage of the bronchi of human beings with amounts of 15 cc of the following solutions for a total of 250 cc with the last 15 cc left in for prolonged disinfection, would be without injurious effects at the rate of a treatment every two days or twice a week

Gentian violet	1 2,000
Acridavine	1 2,000 (less irritant than gentian violet)
Merodicein	1 2,000
Mercurophen or metaphen	1 5,000
S T 37	1 2,000 (equal parts of S T 37 solution and saline)
Potassium permanganate	1 500 to 1 1,000
Mild silver protein	1 20
Gomenol	1 10
Chloramine T	1 300
Neoarsphenamine	1 50

Mercurochrome 1 200 is apparently too irritating and may produce renal injury, a 1 25 dilution of a stock 1 per cent solution of iodine in 25 per cent alcohol also produced pulmonary changes, as was likewise true of surgical solution of chlorinated soda. It is to be observed that iodized oil was well tolerated in confirmation of the work of Stiehm and the Ballons, but is too low in bactericidal activity to be used for bronchial disinfection

#### COMMENT AND PRACTICAL APPLICATIONS

It would appear, therefore, that bronchial disinfection may be attempted in the treatment of bronchiectasis and other types of suppurative pneumonitis by lavage with disinfectant solutions. In this connection the chosen disinfectant may be incorporated in the Bledsoe-Fisher hypertonic saline solution previously mentioned, and amounts of 15 cc slowly passed through into the main bronchus coincident with each inspiration, followed by expulsion of the solution together with the thick ropy secretions by the cough reflex until as much as 100 to 250 cc have been used for lavage according to the principles of the Stitt-Wooding method. Following the last lavage, I believe that it will be safe to leave 15 cc in the bronchi for wider distribution and more prolonged bactericidal action

Since frequency of application is undoubtedly a matter of primary importance, I hope that it will be possible to apply the treatment at daily intervals, in some instances for several days at least, followed by

subsequent treatments every two days or several times a week according to conditions. This is a matter, however, to be determined by clinical experience, all that I have hoped to show by the work summarized in this paper is that it would appear possible to employ safely a number of compounds in solutions of sufficient bactericidal activity in the presence of exudates to offer some hope of bactericidal and bacteriostatic activity along with the removal of purulent exudates by lavage as part of a program for the treatment of at least some cases of suppurative pneumonitis.

From the standpoint of choice of compound, no one has stood out predominantly among those employed in this study. But it would appear that the following are worthy of trial:

- (a) Equal parts of 1:2,000 gentian violet and 1:2,000 acriflavine
- (b) Mercurophen or metaphen 1:5,000
- (c) Merodicein 1:2,000
- (d) Equal parts of hexylresorcinol solution 1:2,000 (S.T. 37) and saline solution
- (e) Mild silver protein 1:20
- (f) Chloramine T 1:300
- (g) Neoarsphenamine 1:100 for spirochetic infections

Each compound may be prepared with the Bledsoe-Fisher hypertonic saline solution, and the chosen solution should be warmed to about 40°C before administration.

According to my results, these compounds in the strengths mentioned are bactericidal in the presence of pus, do not destroy leukocytes or retard phagocytosis, appear otherwise to fulfil most of the requirements of an ideal antiseptic as previously outlined, and will probably be well borne by human beings although the latter must be determined by clinical experience, as must the choice of the compound to be employed.

If the method is given clinical trial, the results may be judged not only by the condition and progress of the patient with special reference to the character and quantity of expectoration but by qualitative and quantitative bacteriologic examinations of the bronchial secretions. That is to say, it is readily possible to determine quantitatively with approximate accuracy the influence of treatment on the numbers of viable bacteria in the secretions by plating methods. Where spirochetes greatly predominate, it would appear possible to use intrabronchial lavage and injections of neoarsphenamine in 1:50 or 1:100 dilution and study the effects by examination of direct smears of the secretions supplemented by dark-field examinations.

## SUMMARY

1 Further investigations into the etiology and treatment of the chronic bronchitides, extensive bronchiectasia and other nontuberculous suppurative infections of the bronchi and lungs would seem to be demanded because of the frequency of these conditions and the invalidism resulting therefrom

2 Streptococci, staphylococci and other pyogenic organisms appear to be of primary etiologic importance with the possibility of spirochetes and pathogenic molds possessing primary or secondary importance in some cases

3 The principles of chemotherapeutic disinfection by intrabronchial treatment with chemical agents are discussed, likewise, the possible dangers and contraindications to bronchial disinfection by the local or topical application of chemical agents by bronchial lavage

4 A large number of disinfectants have been studied for bactericidal and spirocheticidal activity in vitro in a menstruum rich in protein for the selection of compounds for bronchial disinfection. Several have been found apparently suitable for this purpose

5 Intratracheal injections of iodized oil in rabbits followed by roentgenographic examinations have shown that it is possible to secure a wide intrapulmonary distribution of solutions of chemical disinfectants by this route of administration

6 The toxicity of a large number of chemical disinfectants has been determined in rabbits by intratracheal injections of 1 cc per kilogram of weight every two days. The approximate maximum tolerated doses of from six to twenty-four injections are given

7 The pathologic tissue changes produced in the trachea, bronchi, lungs and kidneys of rabbits receiving intratracheal injections of various disinfectants are presented

8 It has been found possible to give repeated intratracheal injections of various disinfectants in bactericidal concentrations with no, or but slight, injury to the bronchi and lungs of rabbits

9 Suggestions and a method are presented for the clinical trial of bronchial disinfection by lavage with any one of several chemical agents in the treatment of selected cases of bronchiectasis and other types of suppurative pneumonitis

# PRODUCTIVE-CICATRICIAL SYPHILITIC DISEASE OF THE PULMONARY ARTERY

HOWARD T KARSNER, M D

CLEVELAND

Syphilis may affect the pulmonary artery as a productive-cicatricial lesion like that form common in the aorta, the so-called Dohle-Heller type, it may occur as a gummatous arteritis, or it may be manifested simply by the formation of gummas. Warthin further accepted as syphilitic a form of diffuse arteritis which affects principally the smaller vessels. Neither he nor Bruning, Thorel, Henschen or Rogers, all of whom he quoted in support of this view, offered definite or convincing proof. The conclusions of these investigators were arrived at by probability, exclusion or belief, based occasionally on the finding of syphilitic lesions elsewhere in the body. In spite of Peck's excellent critique of the matter, the recent report of a case by Hare and Ross is based on the presence only of suspicious lesions in the systemic aorta. These authors quoted Thomas in support of their conclusion, but many of Thomas' cases did not come to autopsy, and he reported two cases of intimal sclerosis of the pulmonary artery which he suggested were of syphilitic origin because of a history of syphilis, in one of these the Bordet-Wassermann test was twice negative and never positive! Rosenthal did not include syphilis in his theory of the pathogenesis of sclerosis of the smaller pulmonary arteries.

Peck analyzed the cases of syphilitic involvement of the pulmonary artery reported up to 1927. He accepted only twelve as definitely syphilitic. Nine of these showed either simple gumma formation or gummatous arteritis. The other three, one each reported by Barth, Henschen and Warthin, were indubitable cases of productive-cicatricial disease of the main pulmonary trunk. Peck accepted two other cases as manifestations of the extension of syphilitic lesions from the mediastinum to the pulmonary artery. The remaining fifteen cases were regarded as not proved.

A somewhat more liberal view than that of Peck would admit one of the cases that he regarded as doubtful, namely that of Ploeger. The case reported by Letulle and Jacquelin, apparently overlooked by Peck, although poorly described in the gross, was characteristic microscopically. The same may be said of one of Thomas' cases (included in his category of pure or primitive pulmonary arteritis). Since Peck's publi-

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From the Institute of Pathology, Western Reserve University, and University Hospitals



cation, Plenge, who acknowledged the validity of Peck's criteria, has reported two cases of productive-cicatricial syphilitic disease of the pulmonary artery. One of Sindoni's cases may also properly be included, and the same is true of that of Reeke<sup>1</sup>. The case reported by Darre and Albot was not proved to be syphilitic. The present report is that of a case of unquestionable productive-cicatricial syphilitic disease of the pulmonary artery. The cases which may now be included in the group of this type of disease are shown in the accompanying table.

*Cases of Productive-Cicatricial Syphilitic Disease of the Pulmonary Artery*

Author	Age	Sex	Dilatation	Saccular Aneurysm	Syphilitic Aortitis
Henschen	42	F	+	?	—
Barth	57	M	—	+	—
Ploeger	52	F	+	+	+
Warthin	37	M	—	+	+
Letulle and Jacquelin	58	M	+	—	—
Thomas	38	M	+	—	?
Sindoni	42	F	+	—	+
Reeke	58	F	+	—	+
Plenge	28	F	+	—	—
Plenge	40	M	+	—	+
Karsner	28	F	+	—	+

Peck drew attention to the fact that among the twelve cases that he accepted as definitely syphilitic, nine were of gummatous type and three of productive-cicatricial type, a reversal of the proportions in aortic syphilis. If the cases in the table be accepted, the instances of both types of disease in the pulmonary artery are about equal. Even this interpretation would still leave the proportion of gummatous lesions of the pulmonary artery far higher than that of gummatous lesions of the aorta. The three cases accepted by Peck showed saccular aneurysm. The case of Reeke and the two cases of Plenge would be accepted under the strictest criteria, and these three cases were not accompanied by saccular aneurysm formation. In all instances, however, some form of definite dilatation of the artery was observed. In one of Plenge's cases the inner layers of the pulmonary artery were destroyed, and there was a dissecting aneurysm which had ruptured into the pleura.

Six of the eleven patients were women. Four were in the sixth decade, two in the fifth, three in the fourth and two in the third. The ages were from 28 to 58 years, with two cases at each of these extremes. Five patients were 40 years old or less, and six patients were more than 40 years old.

#### CLINICAL ABSTRACT

*History*—The patient, a mulatto woman, married, 28 years old, was admitted twice to Lakeside Hospital in the service of Dr. Joseph T. Wearn. Her father and mother were dead, of unknown cause. One sister died of "pneumonia" at 22.

1 Von Glahn has the protocol of an unpublished case in the records of the Department of Pathology, Columbia University, New York.

years of age. The patient had measles, mumps and pertussis in childhood and influenza in late adolescence. She was married at 18 years of age and had three pregnancies, each of which terminated spontaneously at about two and a half months. She had not been well since her last abortion in May, 1929, when she first noticed coldness and numbness of the upper extremities. In February, 1930, she noted dizziness, shortness of breath and a sensation at the nuchoid described as a "pulling-down feeling." She had periods of nausea and vomiting and a slight cough, but neither hematemesis nor hemoptysis. She had lost about 20 pounds (9 Kg.) in the six months preceding hospitalization.

Physical examination on her first admission, on June 18, 1930, showed distention of the veins in the right side of the neck, marked pulsation of the right carotid with a to and fro murmur and slight enlargement of the cervical and axillary lymph nodes. The chest moved poorly and there was enlargement of the upper mediastinal area of dulness to the left, but the lungs were clear. The left border of the heart was just within the anterior axillary line and the right border at the right sternal margin. A systolic murmur was heard at the apex, and a soft to and fro murmur suspected over the aortic area. Neurologic and general physical examination otherwise gave no significant results.

Roentgenologic examination of the chest showed marked transverse enlargement of the heart, with an unusually high aortic knob, obliteration of the incisura and, in the first oblique view, a slight compression of the trachea. The second oblique view showed localized dilatation of the aorta in its upper portion. The fluoroscope showed marked dilatation at the root of the aorta. The arteries of the arms did not pulsate, the blood pressure was not determined, and it was considered that the aortic dilatation was probably of syphilitic origin.

The urine was not abnormal. The white blood cell count was 11,900 and 9,200, and one differential count showed no abnormalities. On one occasion the blood showed 60 per cent hemoglobin (Sahli) and 5,000,000 red cells, with numerous macrocytes, slight anisocytosis and poikilocytosis, and central pale staining. On another occasion the hemoglobin was 65 per cent. The temperature ranged generally between 37 and 38 C (98.6 and 100.4 F), the pulse rate between 50 and 70 and the respirations between 20 and 25 with occasional records of as high as 30 per minute. The Wassermann test was 4 plus positive. The patient was kept in bed and in a wheel chair, complained of occasional pains in the left side of the chest, was treated symptomatically, without antisyphilitic measures, and at her own request was discharged on August 17.

At her home she was unable to be about much. In December she noticed swelling of both legs and thighs. A cough developed and became gradually worse. Early in October, 1931, she began to have chilliness, sweats and fever. She entered Lakeside Hospital on November 27, with the additional statement that she had lost 11 pounds (4.9 Kg.) in the preceding two weeks. At this time the edema had disappeared. The heart showed marked enlargement to the right and left, and a systolic murmur over the pulmonary area was transmitted to the entire left lung. The lungs showed the signs of consolidation and cavitation in the left upper lobe. Blood pressure in the thigh was 146 systolic and 85 diastolic. During this period in the hospital the patient's temperature was generally between 38 and 40.1 C (100.4 and 104.9 F), the rises occurring in the late afternoon or evening, with one drop to 36.5 C (97.7 F) and two elevations to 41 C (105.8 F). The pulse rate was generally about 120, with a terminal elevation to 150. The respiratory rate fluctuated widely, but was generally about 30. The urine showed albumin, occasional erythrocytes and leukocytes and many casts. The output of phenol-sulphonphthalein was 45 per cent in two hours. The leukocytes in the blood num-

bered 9,250 and 13,700, the differential counts showed a slight increase in polymorphonuclears. The erythrocyte counts were 3,390,000, 4,650,000 and 4,100,000, with no note on the character of these cells. The vital capacity was 1,800 cc. The spinal fluid was normal. A culture of the blood showed no growth. The stools were normal. The sputum contained many acid-fast bacilli. The blood for the Wassermann test was anticomplementary, but the Kline microprecipitation test was 4 plus positive. Roentgenologic examination at this time showed nothing significantly different from the former examination as regards the heart and great vessels, but the entire left lung showed irregularly distributed density, most marked in the upper portion, which was associated with cavitation. The right lung showed density in the peritruncal region. Electrocardiograms showed simple tachycardia and inversion of the T wave in lead III. The course during this stay in the hospital was progressively downward. Four days before death, symptoms of meningeal irritation appeared, but the fluid obtained by lumbar puncture was normal. The patient died on November 18.

*Summary*—Nineteen months elapsed between the appearance of symptoms and death. It is suggested that syphilis was contracted at the time of the patient's marriage, thirteen years before death. It was reasonably established that the patient had syphilitic aortitis with either dilatation or aneurysm, and that at some time during the last nineteen months of life, tuberculosis of the lungs developed, which was especially manifest on the left side. The explanation of the to and fro murmur in the right carotid, the absence of pulse in the arteries of the arms and the later development of a systolic murmur of the pulmonic area, transmitted to the left lung, were the subject of much discussion. Doubt as to the presence of aortic aneurysm made it difficult to assume that an aneurysm was the cause of these disturbances, and it was suggested that there was congenital anomaly of the subclavian vessels.

After the actual condition was disclosed at autopsy, Dr David Steele reviewed all the roentgenograms and found in one plate taken at a distance of 7 feet (213 cm) in November, 1930 (fig 1), that the obliteration of the cardiac incisura was distinguishable from that of the aortic knob by means of a shadow and because of the oblique views, probably not due to the left atrium. A shadow at the right hilus was indicative of dilatation of the right pulmonary artery. This plate also showed the first evidence of pulmonary tuberculosis. The findings are like those described in pulmonary artery dilatation by Balaban and Pokydow, considered adequate for a diagnosis by Vogl, and they conform to the picture of pulmonary hypertension given by Thomas.

*Autopsy*—The autopsy, limited to the thorax and abdomen, was performed four hours after death by Dr H. M. Dixon. The body was that of a fairly well nourished, well developed colored woman, approximately 28 years of age, 165 cm in length and about 60 Kg in weight. The body was still warm, showed slight rigor mortis of the extremities and no livor mortis. External examination showed nothing noteworthy except slight enlargement of the cervical lymph nodes and moderate edema of both feet and ankles, more marked on the left side.

The primary incision showed nothing noteworthy. The peritoneum and viscera were normal except that the liver extended 5 cm below the costal margin. In the thorax the heart extended 3 cm to the right of the midline and beyond the mid-axillary line to the left. The left pleura was completely, and the right partly, obliterated by fibrous adhesions.

*Cardiovascular System* The pericardial sac and fluid were normal. In the anterior mediastinum the great vessels were bound together by dense fibrous adhesions.

The heart was of globoid shape and, free from blood and clot, weighed 430 Gm. The epicardium and subepicardial fat were normal, the coronaries were not tortuous. The muscle was firm, cut with normal resistance and showed a slightly bulging, moist, uniformly dark red cut surface. The left ventricle was 7 cm long and the wall 15 mm thick. The right ventricle was 11 cm long and the wall 4 mm thick. The trabeculae carneae and the papillary muscles were large and slightly flattened. All four chambers appeared to be moderately enlarged, but this was most striking in the right ventricle. The mural and valvular endocardium was normal throughout, save for the pulmonary cusps to be described. The mitral orifice was 9 cm in circumference, and the tricuspid 12 cm. The

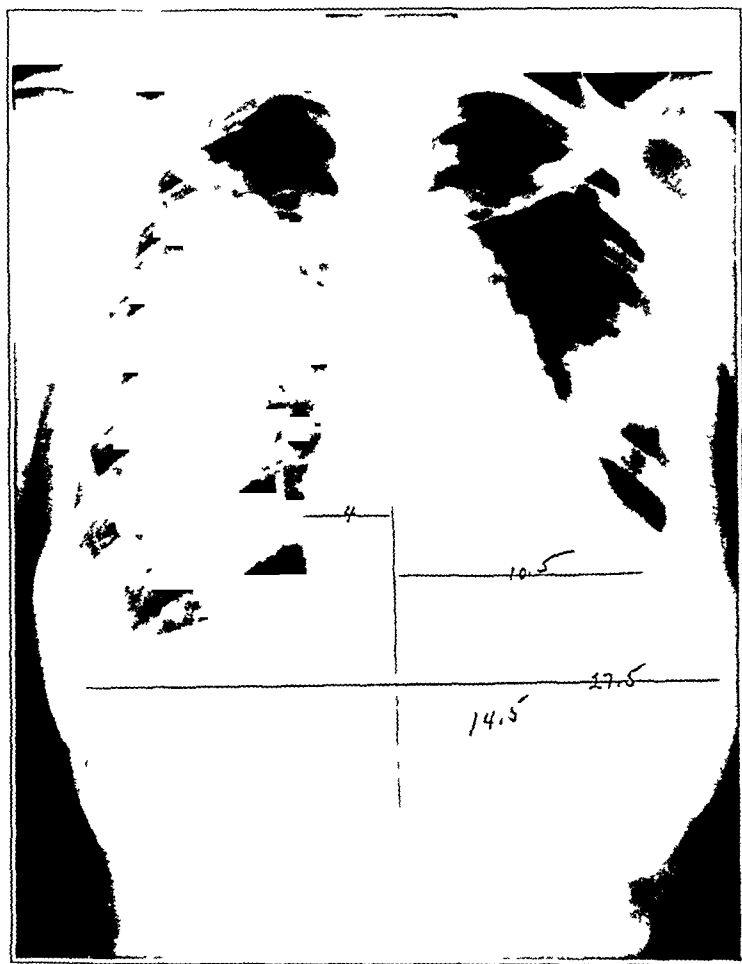


Fig 1—Roentgenogram taken at a distance of 7 feet following the patient's second admission. Note the obliteration of the cardiac incisura, the shadow of the right pulmonary artery and the shadows of tuberculous involvement of the left lung.

foramen ovale was closed and there were no gross lesions of the conduction system. The coronaries showed a few small plaques of thickened yellow and gray intima. The orifices were normally patent.

The aortic orifice measured 6 cm in circumference, and the leaflets and sinuses of Valsalva were normal. The aorta was normal for a distance of from 4 to 5 cm above the ring, save for a small plaque of intimal thickening from 3 to 5 mm in diameter, elevated about 1 mm above the surface, smooth, well defined and of a gray color, situated in the right posterior wall, 3 mm above the junction of the anterior and right posterior leaflets. Beginning from 4 to 5 cm above the ring the aortic circumference increased abruptly to a measurement of 82 cm. Beginning

at this region, in an irregular line extending horizontally around the aorta, the vessel showed the characteristic morphology of syphilitic mesaortitis, which terminated abruptly at the isthmus aortae, where the circumference was reduced to 4 cm. Beyond this the aorta measured 4.4 cm in circumference and exhibited a moderate intimal atherosclerosis. In the syphilitic area two small saccular aneurysms were found, the orifice of each about 3 mm in diameter. One in the inferior surface of the arch was 12 mm deep, and the other in the posterior aspect was about 7 mm deep. Both were filled with a thrombus. The innominate and left subclavian arteries at their origin showed markedly thickened walls, the lumen

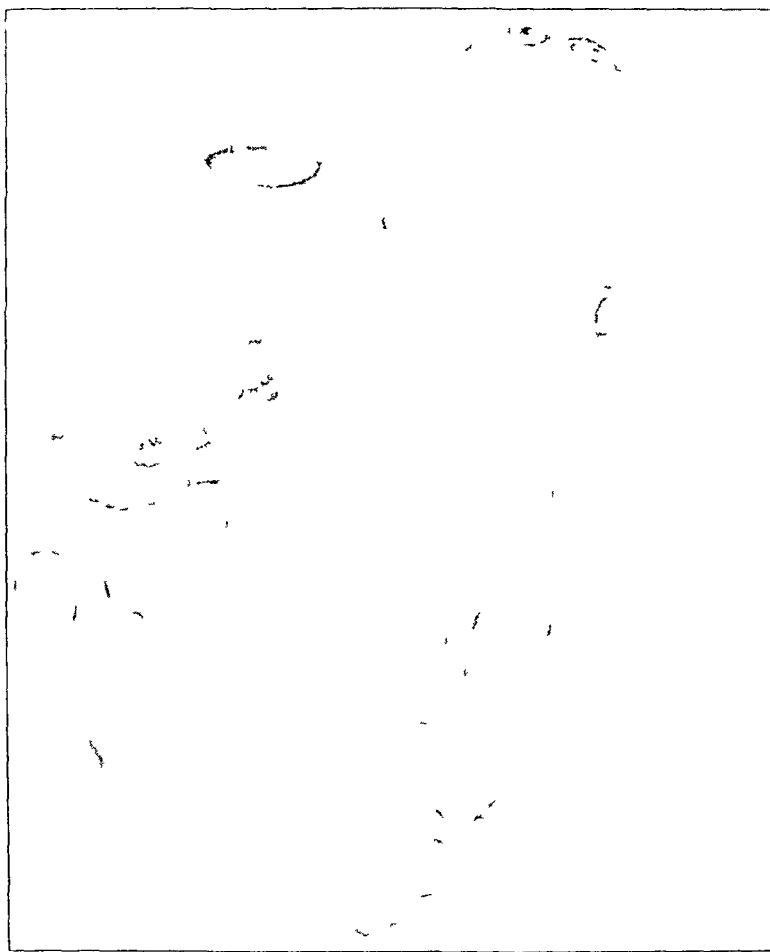


Fig 2—Anterior view of the heart, showing dilatation of the aorta and pulmonary artery, disease of the branches of the aortic arch and occlusion of the left pulmonary artery

was reduced to less than 1 mm in diameter and the orifice of each was occluded by a thrombus. The left carotid orifice was similarly but less stenotic and without thrombus. The distal portion of these arteries was normal.

The pulmonary orifice was 8 cm in circumference. The leaflets were thin, transparent and pliable. The arterial surface of the adjacent parts of the anterior cusps was closely applied by firm fibrous tissue to the arterial wall, so that this commissure was 8 mm wide and exhibited a pale blue, thick, wrinkled intima. Beginning in the sinuses of Valsalva and extending through the entire main trunk of the pulmonary artery, there were the characteristic changes of syphilitic mes-

arteritis The vessel was dilated in spindle form to a maximum circumference of 8.8 cm. The entire wall was thickened, and the intima showed pale blue hyaline plaques of thickening interspersed with areas in which there were stellate and parallel lines of depression, giving the usual wrinkled appearance. There were no localized dilatations, nor was there atheroma or calcification. At its ostium the left branch showed complete obliteration, which extended to the hilus of the lung. Viewed from the main trunk this ostium appeared as a small pitlike depression without a grossly observable lumen. A cross-section midway between the ostium

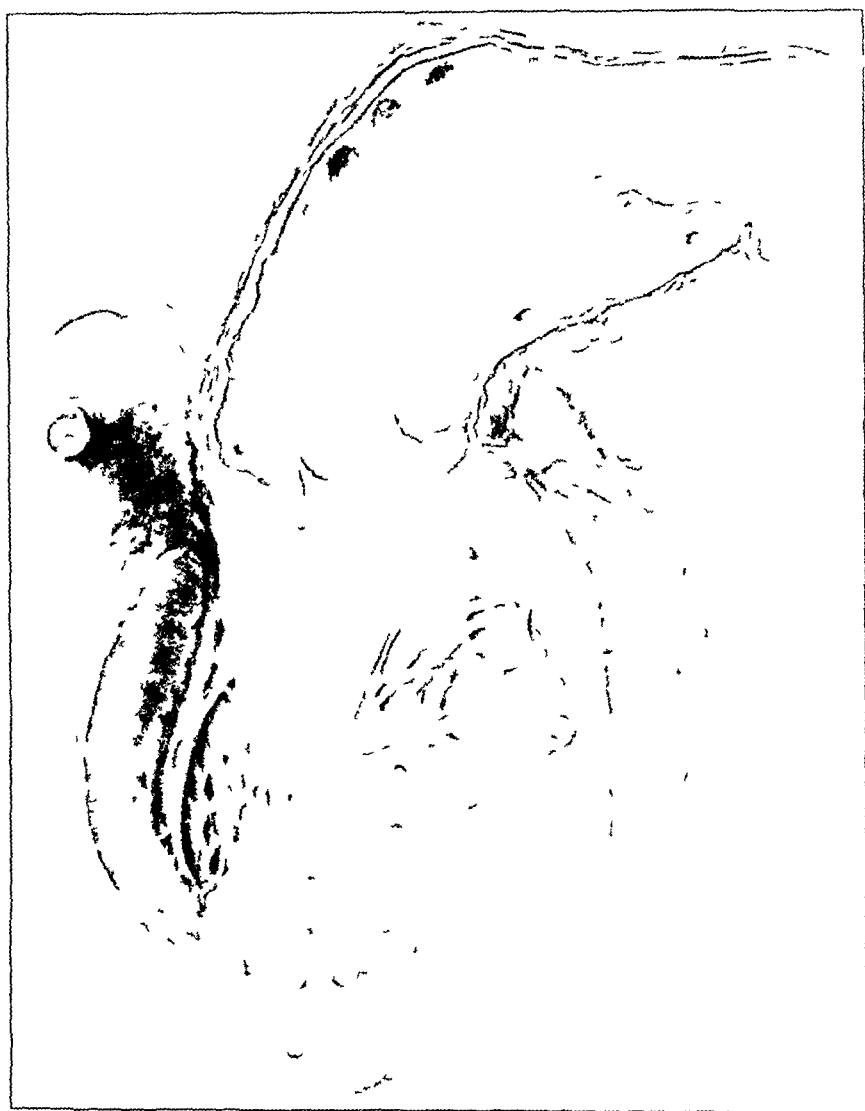


Fig 3—Interior of the left side of the heart and aorta. Note the occlusion of two of the branches of the aorta, partial occlusion of the third and dimples at the site of the two small aneurysms in the sharply delimited syphilitic mesoarteritis.

and hilus showed the obliteration to be caused by dense, pale gray, fibrous tissue in which the intima could not be distinguished. The media was seen as a fairly regular pale yellow circle, interrupted by foci of tissue like that which obliterated the lumen. Marked adventitial and perivascular fibrosis bound the artery firmly to the veins and surrounding tissues. The obliteration ended abruptly at the division of the left pulmonary artery and was replaced by a partly occluding thrombus which extended a short distance into the branches. Grossly it appeared

to be partly organized, but microscopically the organization was only slight. The right branch showed the syphilitic process only at its origin. It was dilated to a diameter of 3 cm.

The right lung weighed 350 Gm, showed fibrous tags of adhesion on the surface, a small tuberculous cavity in the apex and slight passive hyperemia. The bronchi and hilar lymph nodes were not abnormal.

The left lung weighed 640 Gm, and was covered by extensive fibrous tags and moderately thickened pleura. The upper lobe showed extensive intercommunicating tuberculous cavities and caseous pneumonia. The lower lobe showed

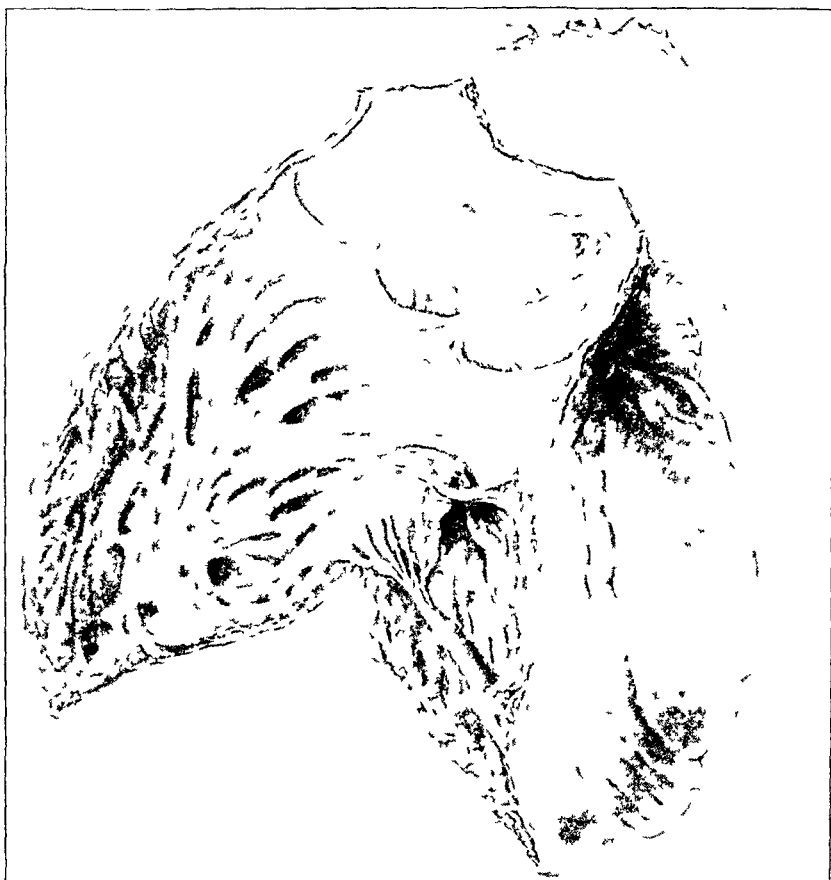


Fig 4—Interior of the right side of the heart and pulmonary artery. Note the obliteration of the commissure between the anterior cusps of the pulmonic valve, typical syphilitic mesarteritis beginning in the sinuses of Valsalva and the dimple at the site of the orifice of the occluded left pulmonary artery.

a tuberculous cavity, 2 cm in diameter. Aside from passive hyperemia there was nothing else noteworthy.

The abdominal viscera showed moderate passive hyperemia. Save for slight tortuosity of the tubes, the genitalia were normal.

A postmortem culture of the blood showed no growth.

**Microscopic Examination** The aorta in the arch showed a thick fibro-hyaline intima, in which were a few fat spaces. The media showed numerous densely fibrous scars about the vasa vasorum, with slight infiltration of lymphoid cells (also a few plasma and large mononuclear cells) and moderate interruption of the

elastica The adventitia was fibrous and edematous The adventitial vasa vasorum showed chronic endarteritis and a moderate perivascular cellular infiltration In the periaarterial fat there was a moderate diffuse infiltration of lymphoid cells In the neighborhood of the small aneurysms the medial and adventitial changes were much more severe The depths of the aneurysms showed practically complete loss of media The larger aneurysm contained a mature thrombus without organization A section of the abdominal aorta showed intimal atherosclerosis without any indication of syphilis

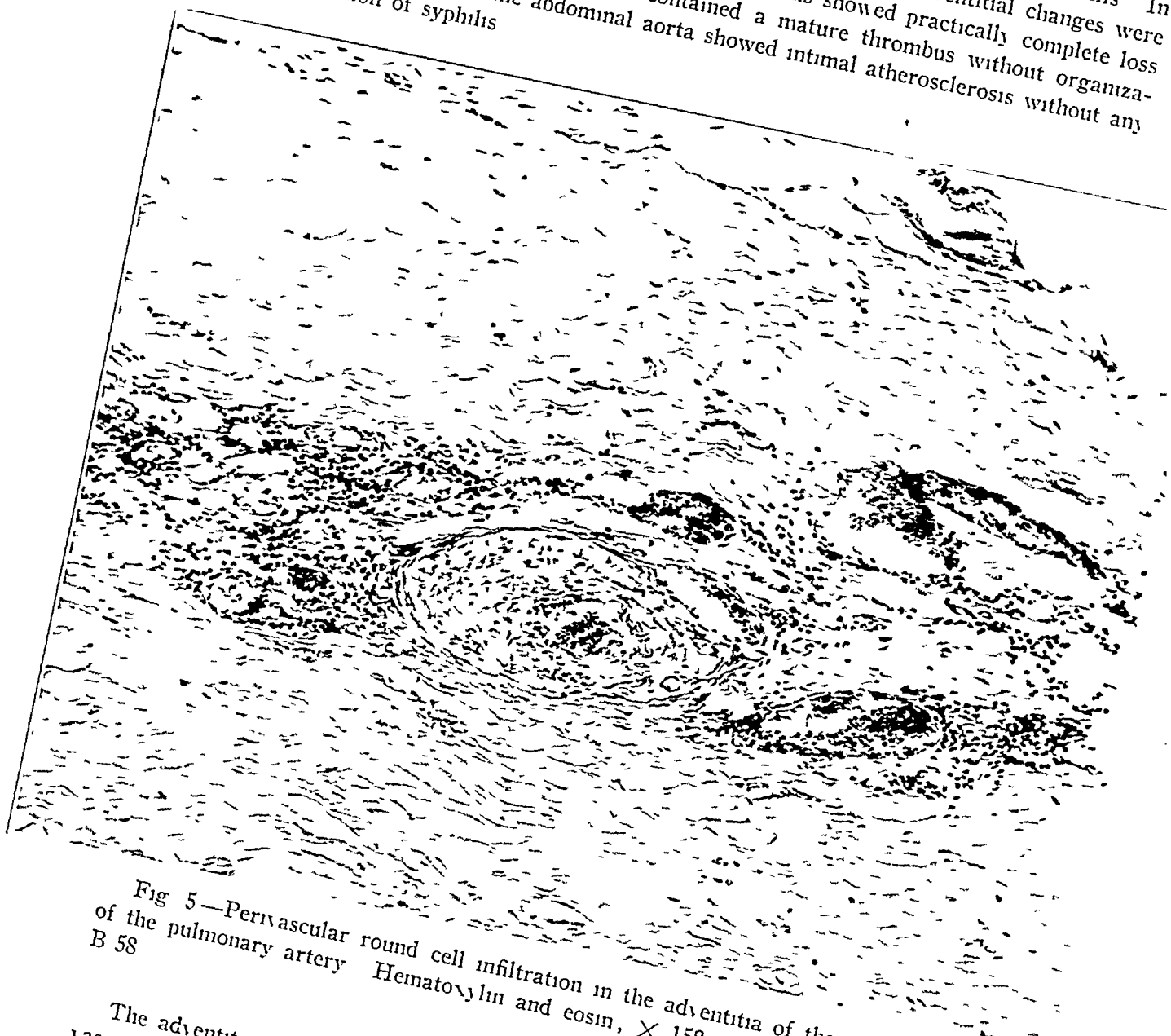


Fig 5—Perivascular round cell infiltration in the adventitia of the main stem of the pulmonary artery Hematoxylin and eosin,  $\times 158$  Wratten green filter B 58

The adventitia of the innominate artery showed intimal thickening of the vasa vasorum and extensive perivascular infiltration of lymphoid cells with a few plasma and large mononuclear cells Where these vessels extended into the periphery of the media the same changes were noted The media was of irregular thickness and showed a diffuse, and in a few places a focalized, infiltration of lymphocytes and a small number of large mononuclears The intima was not distinguishable from a mass of collagenous connective tissue which filled the entire former lumen of the artery sometimes densely and sometimes loosely arranged Numerous



endothelial-lined blood vascular spaces of variable size were present, and two showed a thin musculo-elastic coat. Elastica stain showed only small fragments of the internal lamina and numerous interruptions in the elastica of the media. The central mass of fibrosis showed a few granules of blood pigment.

The subclavian artery showed essentially the same changes as the innominate, except that the tissue within the lumen was more loosely arranged, there were suggestions of fibrin remnants, the canalization was by larger vessels and the perivascular infiltration of lymphocytes was less marked.



Fig 6—Fragmentation of the elastica of the main stem of the pulmonary artery. Verhoeff-Masson trichrome (acid fuchsin, ponceau de lyldine, licht Grün),  $\times 117$ . Wratten orange filter E 22.

The pulmonary trunk showed marked thickening of the intima by fibrous connective tissue in which a few fat spaces and a small amount of mucoid tissue were observed. There was no clearly defined internal elastic membrane. The media showed a few areas of what appeared to be small fibrous scars and irregular areas of interruption of elastica. A few small areas of lymphoid cell infiltration often approximated the scars. The adventitial arteries showed intimal fibrosis and moderate perivascular lymphoid cell infiltration. The intrapulmonic branches,

from 0.5 to 1 mm in diameter, showed moderate intimal fibrosis. The branches, of about arteriolar and slightly larger size, in the neighborhood of the tubercles only, showed a loosely fibrous thickened intima with lymphoid cell infiltration of the media and intima, but this was not general throughout the lungs.

The left main branch was sectioned at two levels in the area of occlusion. The lumen in one section was filled with hyalinized fibrous tissue with a few granules of blood pigment, and in the other with dense connective tissue in which there were a few endothelial-lined blood channels. Otherwise the sections were similar.



Fig 7—Perivascular and perineurial round cell infiltration in the adventitia of the left pulmonary artery. Hematoxylin and eosin,  $\times 158$ . Wratten green filter B 58.

The internal elastic lamina was present only as small fragments, some of which were swollen. The elastica of the media showed large areas of interruption and disappearance, and many fragmented fibrils were swollen. The interruption of elastica was by a mass of fibrous tissue with many fibroblasts, small blood vessels of capillary size and a diffuse infiltration of lymphoid cells, a few plasma cells, many large mononuclears and a notable number of polymorphonuclear cells, the whole giving the impression of a granulation tissue. The adventitia showed heavy masses of dense fibrous, partly hyaline, connective tissue. The vasa vasorum

showed variable degrees of intimal fibrosis. Marked perivascular and perineurial infiltration of lymphoid, plasma and large mononuclear cells was present.

Sections stained by a modification of the Warthin-Starry method, which showed spirochetes in controls of syphilitic fetal liver and syphilitic testis of the rabbit, failed to demonstrate spirochetes in any of this material.

The myocardium showed large muscle nuclei with square ends, loss of muscle striations and attenuation of the fibers, and a diffuse fibrosis, slight in extent and somewhat more marked about the vessels, with a few lymphoid and plasma cells. The lesions showed no definite characteristics of syphilitic myocarditis. The coro-



Fig 8—Diffuse round cell infiltration of the media of the left pulmonary artery. Hematoxylin and eosin,  $\times 158$ . Wratten green filter B 58.

nary arteries were sectioned at various levels, including a point within 2 cm of the orifice, and although showing definite intimal fibrous sclerosis they exhibited none of the changes described by Moritz in syphilitic coronary arteritis.

The lungs showed characteristic tubercles, tuberculous caseation and well marked passive hyperemia. The branches of the pulmonaries have already been described. The pleura of the left lung was markedly thickened by fibrous connective tissue, somewhat loosely arranged and with a slight diffuse infiltration of lymphocytes. Especially notable was a rich vascularization of visceral and parietal

pleura in all sections from the left side. The vessels were extremely numerous and many were well differentiated into small arteries and veins.

The other organs, especially the liver, spleen and kidneys, showed a much more marked passive hyperemia than was evident in the gross specimens.

*Summary*—The significant autopsy findings were marked syphilitic arteritis of the arch of the aorta and the main trunk of the pulmonary artery<sup>2</sup>. In the aorta the process was accompanied by fusiform dilatation, small saccular aneurysms and syphilitic arteritis of the three branches from the arch with completely organized,

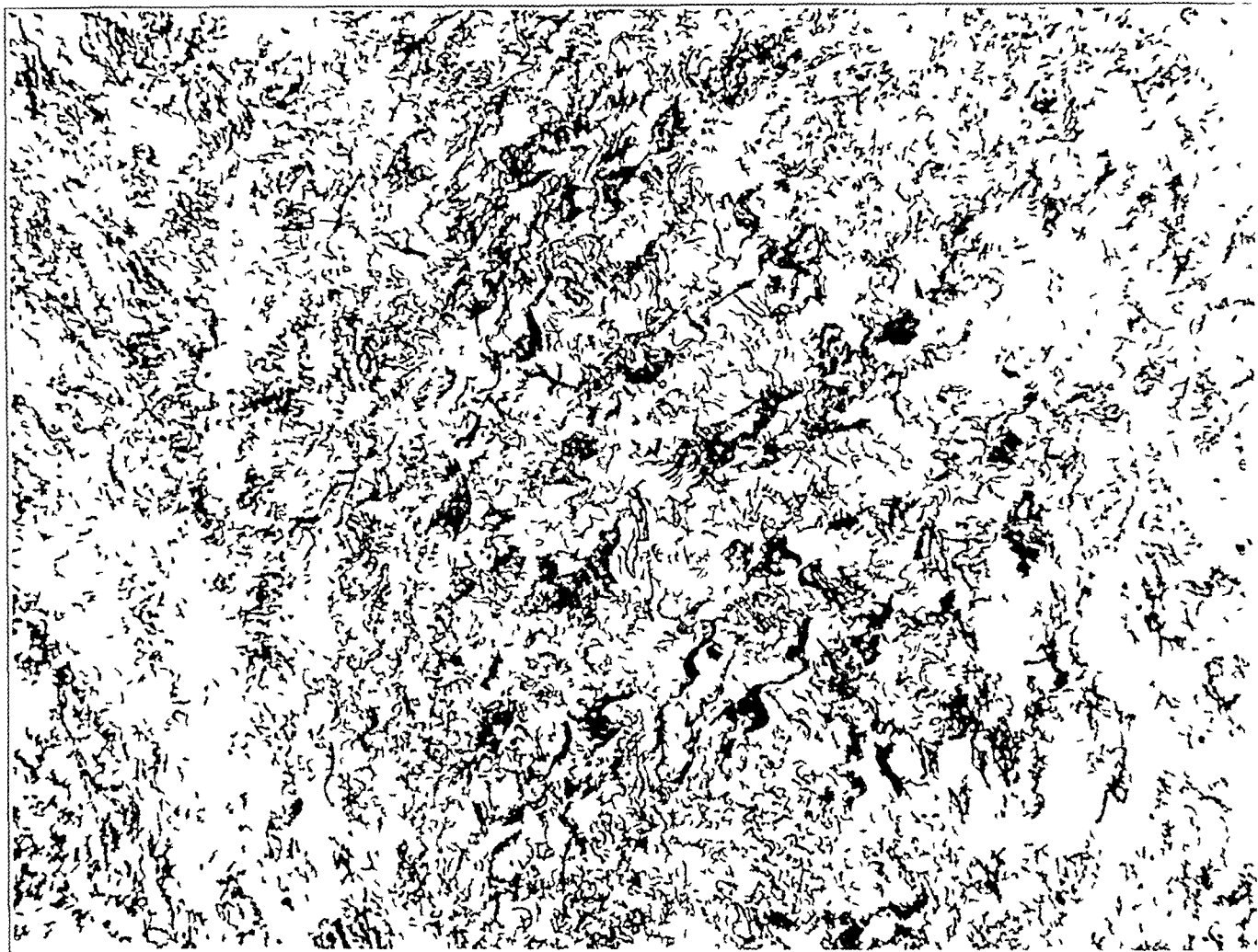


Fig 9—Fragmentation and swelling of elastica of the media of the left pulmonary artery. Verhoeff-Masson trichrome (as in figure 6),  $\times 117$ . Wratten orange filter E 22.

cicatrized, canalized thrombosis of the innominate and subclavian arteries. In the pulmonary artery the process was accompanied by fusiform dilatation, organized

<sup>2</sup> The morphologic diagnosis is as certain in the pulmonary artery as in the aorta. With his skill and excellent technic Warthin was able to demonstrate spirochetes, but in the other cases they have not been found. In the present case the demonstration failed, but the morphologic evidence is so definite as to leave no doubt of the diagnosis.

canalized thrombosis of the left branch and dilatation of the right branch. Most careful examination failed to disclose enlargement of the bronchial arteries. There was moderate hypertrophy of the heart, especially manifest in the left ventricle and also present in the right ventricle, associated with cardiac dilatation, generalized, well marked passive hyperemia and, in the lower extremities, also with edema. There was chronic ulcerative pulmonary tuberculosis, especially marked on the left side. There was extremely rich vascularization of the obliterated left pleura. Gumma formation was not noted in any part of the body. The death of the patient was determined principally by the pulmonary tuberculosis and a moderate congestive heart failure.

*Correlation*—The symptoms on the first admission were in part those of congestive heart failure. The coldness and numbness of the upper extremities, together with absence of arterial pulsation, were due to disease of the arteries derived from the arch of the aorta. The pulsation of the right carotid artery with the to and fro murmur may have been related to incomplete occlusion of the innominate artery at that time. The systolic murmur at the cardiac apex probably belongs among the murmurs of that type frequent in dilated hearts. A to and fro murmur over the aortic area was suspected but not definitely established, and was not recorded during the second stay in the hospital. The development of ulcerative pulmonary tuberculosis was accompanied by the usual cough, chilliness, night sweats, rapid loss of weight, elevated pulse and respiratory rates and reduction of vital capacity. The last sign may have been due in part to passive hyperemia of the lungs. After the second admission a systolic murmur was heard over the pulmonic area, probably due to dilatation of the main stem of the pulmonary artery. The transmission to the left lung may have been determined in part by the solidification of the left pulmonary artery and in part by the tuberculous consolidation in the lung. It is noteworthy that with definite separation of one of the pulmonic commissures there was no diastolic murmur, because the valve must have been incompetent. The inversion of the T wave in lead III is not satisfactorily explained, since the hypertrophy of the right ventricle was only moderate as compared with that of the left ventricle. In cases in which the smaller pulmonary arteries are narrowed and the right ventricle notably hypertrophic, clearcut right axis deviation has been reported, but these anatomic changes were not present in this case. Anemia was not severe at any time. There was no secondary polycythemia and no reason disclosed at autopsy why there should have been. It is possible that had clinical attention been drawn to disease of the pulmonary artery, the roentgenologic examination might have been interpreted as showing dilatation of the main stem of the pulmonary artery in addition to dilatation of the aorta.

#### COMMENT

It may well be true that in the later stages of syphilitic disease and of atherosclerosis of the pulmonary artery, Warthin's statement that the two lesions are difficult to distinguish is valid. In the accepted cases of syphilis, however, the condition of the pulmonary artery is such that the distinction can readily be made. As a rule the perivascular cellular infiltration in the media is less severe than is common in aortic syphilis yet many cases of the latter disease show medial changes which are no different in this respect from those occurring in the pulmonary

artery Adventitial perivascular cellular infiltration is quite as marked as that observed in the aorta The condition of the internal elastic membrane varies in syphilitic aortitis, but the variation seems to be greater in the same disease of the pulmonary artery In the cases described in detail this membrane may be intact, fragmented or completely lost The medial elastic lamellae are interrupted in both instances The swelling of elastica fragments with the formation of spider-like bodies is more marked in the case described here than is ordinarily observed in syphilitic aortitis Granulation tissue with new blood vessel formation in the media is especially notable in the occluded left pulmonary artery in this case, but this may have been due to the action of the thrombus as a foreign body rather than to the syphilitic character of the arterial disease In general, it can be asserted that productive-cicatrical syphilitic lesions of the pulmonary artery show essentially the same changes as those observed in syphilitic mesoaortitis

Of the cases of syphilitic productive-cicatrical disease of the pulmonary artery accepted in this paper, association with similar disease of the aorta is noted in six instances and freedom from aortic lesions in four instances The question arises as to whether or not the lesion of the pulmonary artery in the case here reported represents extension from the aortic disease In fifty-nine cases of aortic syphilis Sindoni found extension to the pulmonary artery in nine With one exception, the disease in the pulmonary artery was slight and often confined to the adventitia It is noteworthy in the present case that the part of the aorta in closest contact with the pulmonary artery was free from aortitis No final conclusion can be reached, but the anatomic evidence in this case is against rather than in favor of the conception of extension from the aorta

If aneurysm be defined as a permanent dilatation of a vessel, all the cases exhibited this lesion, of a cylindric, fusiform or saccular variety If the dilatation must be sharply localized, only three of the eleven cases showed aneurysm formation The significant fact is that the disease in the pulmonary artery in all cases led to dilatation of the vessel, either general or localized or both Although pulmonary hypertension may produce dilatation of the pulmonary artery and its larger branches, as indicated by Thomas, there is no reason for assuming that this is of importance in the dilatation of the main branch in productive-cicatrical syphilis, except when additional extensive disease of the smaller arteries can be demonstrated Henschen argued that since most aneurysms of the pulmonary artery occur between 24 and 42 years of age, and since arteriosclerosis before the age of 42 is usually due to syphilis, it can be supposed that the aneurysms are syphilitic Posselt thought that this might well be an exaggeration In the cases of productive-cicatrical syphilis of the pulmonary artery accepted here, six of the patients were

42 years old or less and five were more than 42 years old, which in no sense supports Posselt. A true saccular aneurysm of the pulmonary artery in a man 31 years old, without any evidence of syphilis was reported by Okkels and Thiekelsen. It seems justifiable to suggest that although aneurysm of the pulmonary artery is frequent in syphilis, it may perhaps be relatively more often a result of atherosclerosis than is aneurysm of the aorta.

Thrombosis is proportionately much more common in association with syphilis of the pulmonary artery than in similar disease of the aorta. Of the three cases of saccular aneurysm, thrombosis was noted in two, namely in those of Henschen and Warthin. Of the other eight cases, thrombosis was noted in five, namely those of Ploeger, Letulle and Jacquelin, Thomas, Plenge (one case) and me. The clot varies from a relatively fresh mass to complete organization and cicatrization. It cannot be said that the roughening of the intima is any greater in the disease of the pulmonary artery than in that of the aorta, there is no clear statement that the physical state of the blood is different, and hence the thrombosis is probably due to a slower flow of blood in the pulmonary than in the systemic circulation, which is emphasized locally by dilatation. The same inference may be drawn from the instances of thrombosis in apparently nonsyphilitic sclerosis, as in the six cases of Brenner and in those of Frothingham, of Jump and Baumann, of Means and Mallory and of others.

Complete occlusion of the right branch was found in the case of Letulle and Jacquelin, and was due to an organized occluding thrombus. In Henschen's case the right pulmonary branch was markedly stenotic as the result of thickening of the walls. In Barth's case the right branch was narrowed to the size of a lead pencil, apparently from surrounding cicatrization. In Ploeger's case the organized thrombus of the main stem extended into both branches, but patent lumens were observed without note as to diameter. In the case herewith reported the left branch was completely occluded by fibrosis, the result of an old thrombus. Although details are lacking in some of the cases reported, the occlusion of a branch of the pulmonary artery is due in large part to the organization and cicatrization of thrombi. If it is remembered that syphilitic aortitis is often accompanied by narrowing of the ostia of coronaries and large arteries of the aorta, it cannot be said that syphilis of the pulmonary artery appears to be more often accompanied by limitation of the lumens of its branches than is syphilitic aortitis, yet the actual occlusion by thrombosis and subsequent fibrosis seems to be more frequent in connection with syphilis of the pulmonary artery than with syphilis of the aorta. In the present case the occlusion of the innominate and left common carotid appears to be due to an organized thrombus but that this may have been secondary to disease of the walls is indicated.

by the stenosis of the left subclavian artery. That similar occlusion of a branch of the pulmonary artery may be secondary to intimal atherosclerosis is illustrated by the case of Means and Mallory.

The changes in a lung incident to complete occlusion of its main artery are less marked than might be expected. In the cases of Henschen, Barth and Ploeger, in which the lumen was still patent, there were no changes in the lungs that could be definitely attributed to circulatory disturbance. In the case of Letulle and Jacquelin the right branch was completely occluded and the lung showed passive hyperemia. The authors made no note of the collateral circulation. In the case of non-syphilitic occlusion reported by Means and Mallory the bronchial arteries were much enlarged. In the case reported here the bronchial arteries were not enlarged, but the obliterated thickened pleura showed an extraordinarily great number of blood vessels, some of which were differentiated into small arteries. In the absence of enlarged bronchial arteries, it is suggested that the collateral circulation was provided through the richly vascularized adherent pleura. It is not likely that a large amount of collateral circulation is necessary for the maintenance of nutrition of the lung substance. Pleural vascularization was noted by Barth, but this was on the left side, and the left pulmonary artery was apparently not occluded.

Statistically, the association of tuberculosis with stenosis or occlusion of the pulmonary artery cannot be established. It is of interest that in Henschen's case the partial occlusion was associated with extensive pleural synechiae and with tuberculous cavities in that lung. In Barth's case the lung on the affected side was normal. In Ploeger's case, in which both pulmonary branches were partly occluded, the right lung was normal, but the left showed old tuberculosis and bronchiectasis. In the case of Letulle and Jacquelin, both lungs showed miliary tuberculosis, but the lung in which the artery was completely occluded showed extensive tuberculous cavitation. In the case reported here the lung in which the artery was occluded showed not only tuberculosis but, on clinical observation, a rapidly progressing lesion. The opposite lung showed relatively little tuberculosis. In Means and Mallory's case tuberculosis was not observed unless a necrotic partly calcified mass, presumably interpreted as old infarct, may have been tuberculous. The suggestion is plain that occlusion of the pulmonary artery may be of significance in the development or extension of tuberculosis in the lung.

Hypertrophy of the heart, especially manifest in the right ventricle but variable in degree, has been observed in all the cases reported. When a diffuse disease of the small pulmonary arteries and arterioles is present, the hypertrophy may be due to pulmonary hypertension. When such disease is not demonstrated, it is difficult to explain the



hypertrophy because there is no reason for assuming that dilatation or aneurysm of the pulmonary artery brings about cardiac hypertrophy when such a result does not follow similar disease in the aorta. The cardiac hypertrophy in the present case is certainly not due to diffuse vascular disease in the lungs. It is probably not caused by the occlusion of the left branch of the pulmonary artery, since it has been shown physiologically by Daly and by Gibbon, Hopkinson and Churchill that 60 per cent of the cross-sectional area of the pulmonary circulation may be obliterated without effect on the arterial or venous pressure. The widening of one commissure of the pulmonic valve may well have predicated an insufficiency, which could serve to explain the observed hypertrophy.

#### CONCLUSION

Productive-cicatrical syphilitic disease of the pulmonary artery, i. e., of the Dohle-Heller type, is extremely uncommon, but occurs often enough to justify its consideration in clinical diagnosis. Eleven cases, anatomically proved by reasonably liberal interpretation, are now on record. Eight of these would be regarded as clearly established by the most exacting criteria. Gummatous types of lesion about equal the productive-cicatrical type in incidence, but this ratio may be changed as additional cases are reported. The proportion of productive-cicatrical to gummatous lesions is markedly higher in the aorta than in the pulmonary artery. All cases of productive-cicatrical lesions in the main stem of the pulmonary artery show local or diffuse dilatation of the vessel. Associated disease of the smaller pulmonary arteries is by no means constant, but all cases have shown some degree of cardiac hypertrophy. Thrombosis is more frequently associated with productive-cicatrical lesions of the pulmonary artery than with the same lesions of the aorta. The anatomic character of the lesion, as it affects both aorta and pulmonary artery is essentially the same, although it is probable that in the pulmonary artery the internal elastic lamina is more severely affected than in the aorta. Both aorta and pulmonary artery show productive-cicatrical lesions in about half the cases, but this does not of necessity mean that the disease in one vessel is an extension from the lesion in the other vessel.

The disease affects the sexes about equally, and has been found at the age extremes of 28 and 58 years, with the maximum incidence in the sixth decade. It is associated with cardiac difficulties and ultimately congestive heart failure, and may exhibit a fairly characteristic roentgenogram. The most frequent murmur is a systolic murmur over the pulmonic area. Occlusion of a main branch of the pulmonary artery appears to have some relation to development and progress of pulmonary tuberculosis on the affected side.

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# EFFECT OF DRUGS ON CARDIAC STANDSTILL INDUCED BY PRESSURE ON THE CAROTID SINUS

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MINNEAPOLIS

In 1866 Czeimack<sup>1</sup> demonstrated that digital pressure of the neck in the region of the vagus nerve caused a slowing of the heart rate in man. He attributed this effect to a mechanical excitation of the vagus nerve. Hering,<sup>2</sup> while making observations on this phenomenon, noted that very slight pressure resulted in marked cardiac inhibition in some instances. These observations led him to doubt the theory of direct vagal stimulation. Hering and his co-workers demonstrated conclusively that the slowing of the heart by digital pressure in the neck was the result of a reflex which originated in a specialized portion of the internal carotid artery, the carotid sinus. It has been observed that the usual response to pressure on the carotid sinus is a moderate slowing of the heart rate, but that in some instances there results a complete arrest of the heart for many seconds. The present report consists of a study of the effect of drugs on patients with prolonged cardiac standstill induced by sinus caroticus pressure.

In a study of the effect of pressure on the sinus caroticus and of the significance of various disturbances in the cardiac mechanism, it was noted that many persons responded repeatedly with a constant type of reaction. This consisted of a prolonged cardiac arrest due to the vagal inhibition of the sinus node. In some subjects this type of response occurred at times while at other times the period of inactivity of the sinus node was interrupted by the formation of new centers of impulse initiation in the junctional tissues or in the ventricles. It was apparent that the prolonged cardiac arrest in the first group depended on two factors: (1) the temporary suppression of the sinus node, depriving the heart of its normal pacemaker, and (2) the failure of formation of new foci of impulse initiation. The elimination of the cardiac standstill might be accomplished by the application of drugs affecting either of

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1 Czeimack, J N. Ueber mechanische Vagusreizung beim Menschen, *Jenaische, Ztschr f med u Naturw* 2:384, 1866

2 Hering, H E. Die Karotissinus-Reflexe auf Herz und Gefasse, Dresden, Theodore Steinkopff, 1927

these factors. Since the inactivity of the sinus node is due to a reflex stimulation of the vagus nerve, the first factor may be approached by the use of atropine. It was apparent that the cardiac arrest might also be abolished by the use of drugs that would tend to increase the function of rhythmicity of the heart muscle, leading to the formation of new centers of impulse initiation.

The subjects who show no tendency toward a spontaneous formation of ectopic rhythmic centers during the suppression of the sinus node permit a direct and objective study of the effect of drugs on the function of cardiac rhythmicity. If the application of a drug abolishes the prolonged cardiac arrest by inducing an ectopic rhythm, it is reasonable to conclude that this drug increases the rhythmic property of the cardiac muscle. The method used in the present study consisted of a control period of observation, recording with electrocardiograms the effect of stimulation of the carotid sinus. Although the effect of stimulation of both carotid arteries was observed, the right carotid sinus was used in the pharmacologic studies, as this produced the more marked reaction. The drug was then administered, and after a suitable period an electrocardiogram was taken again, the effect of stimulation of the carotid sinus being observed. A week usually elapsed between each group of experiments to allow the effect of the previous procedures to pass off. The following drugs were used: atropine, epinephrine hydrochloride, ephedrine, barium chloride, calcium gluconate, digitalis and caffeine.

Subjects showing prolonged cardiac standstill on pressure on the carotid sinus are encountered most commonly among the elderly patients with cardiac disease attending an outpatient clinic. The pharmacologic studies were carried out on a number of such subjects, but most of the observations were made on a patient who was especially favorable for this type of investigation. This subject, H. B., was a man, 70 years of age, who suffered from mild anginal attacks and showed electrocardiographic evidence of coronary disease. Slight compression of the right carotid sinus repeatedly elicited a constant response, which consisted of a period of cardiac standstill varying from 7 to 9 seconds. The electrocardiogram showed no evidence of either auricular or ventricular activity during this period. This reaction could be elicited without discomfort to the patient, and on successive repetitions of the pressure there was no variation in the response. A period of control observation of several months demonstrated a remarkable constancy in the type of reaction (fig. 1). The response to pressure on the carotid sinus was almost immediate, and the period of cardiac standstill never exceeded nine seconds, although the pressure was applied for from ten to fifteen seconds. After the cardiac standstill, there was consistently a normal first beat originating

in the sinus node. This was frequently followed by a single extrasystole. In none of the control records was there any indication of an ectopic beat during the period of stimulation of the carotid sinus. The other subjects who were observed fulfilled the same requirements, with the exception that there was a shorter period of control observation.

#### EFFECT OF DRUGS

*Atropine*—The effect of atropine is illustrated in figure 2. The heart rate varied between 50 and 58 before the administration of the drug. Pressure on the right carotid sinus elicited a cardiac standstill of 7.2 seconds. A subcutaneous injection of atropine sulphate, 2 mg., was given. Twenty minutes after the administration of the drug the heart rate was 68. Pressure on the right carotid sinus resulted in no change in the cardiac rhythm. The fact that the cardiac inhibition is

Fig 1 (patient H. B.)—Lead 2 of a typical control record. *A*, before pressure on the carotid sinus; *B*, the effect of pressure on the right carotid sinus shown at arrow, cardiac standstill of 8.8 seconds.

abolished by paralysis of the vagus nerve indicates that this nerve is the sole efferent path of the reflex. Heiling, by the use of atropine and by vagotomy, has demonstrated this in experimental animals.

*Epinephrine*—The effect of epinephrine was observed in five cases. The results in the subject H. B. are illustrated in figure 3. Before the administration of the epinephrine, pressure on the right carotid sinus elicited a cardiac arrest of 7.5 seconds (fig 3 *B*). Fifteen minutes after the subcutaneous injection of 1 cc. of epinephrine hydrochloride, 1:1,000, another electrocardiogram was taken following the application of pressure to the carotid sinus (fig 3 *C*). It is to be noted that the P wave disappears, and that there is a slight alteration in the ventricular portion of the complex. It is apparent that an idioventricular rhythm has developed from a focus near the auriculoventricular node under the influence of the epinephrine. The rate of the ectopic rhythm is 48, as compared with the sinus rate of 60 a minute. This experiment was

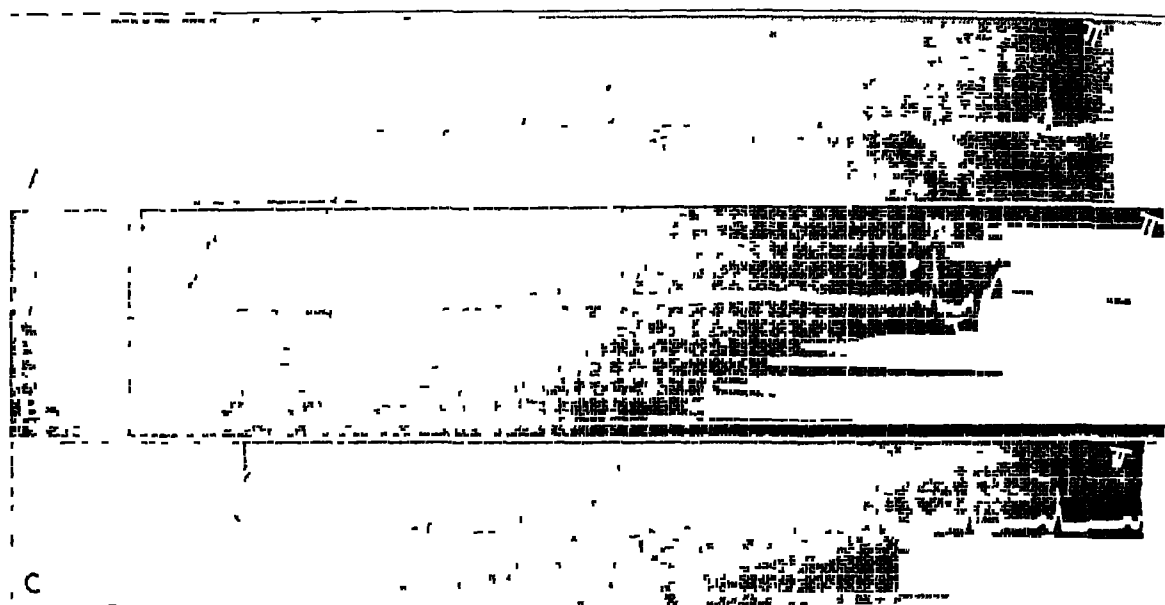


Fig 2 (patient H B) —Lead 2 *A*, before pressure on the carotid sinus, *B*, pressure on the right carotid sinus, with cardiac standstill of 72 seconds, *C*, abolition of the carotid sinus reflex after the administration of atropine sulphate

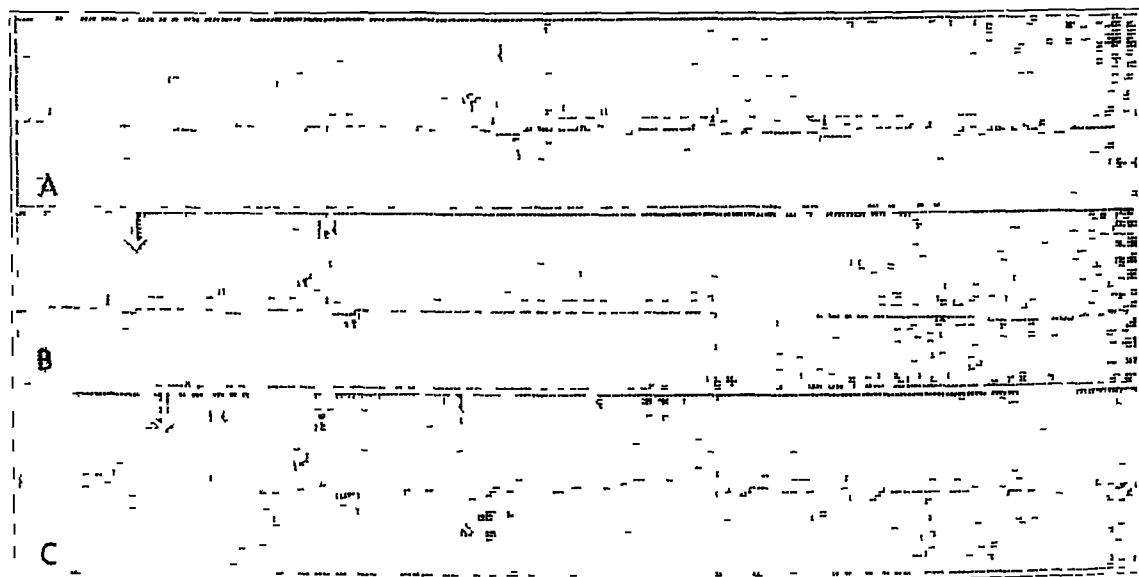


Fig 3 (patient H B) —*B*, the effect of pressure on the right carotid sinus, *C*, compression of the right carotid sinus after the administration of epinephrine, showing the development of an idioventricular rhythm at *X*

repeated on the subject H B on four later occasions, with the same results, the ectopic ventricular beats having approximately the same appearance as those in the first experiment. Four other subjects were studied in the same manner, and in each instance epinephrine abolished a prolonged cardiac standstill by the initiation of a ventricular rhythm (figs 4, 5 and 6). These results confirm the many observations which indicate that epinephrine increases the rhythmic function of the cardiac

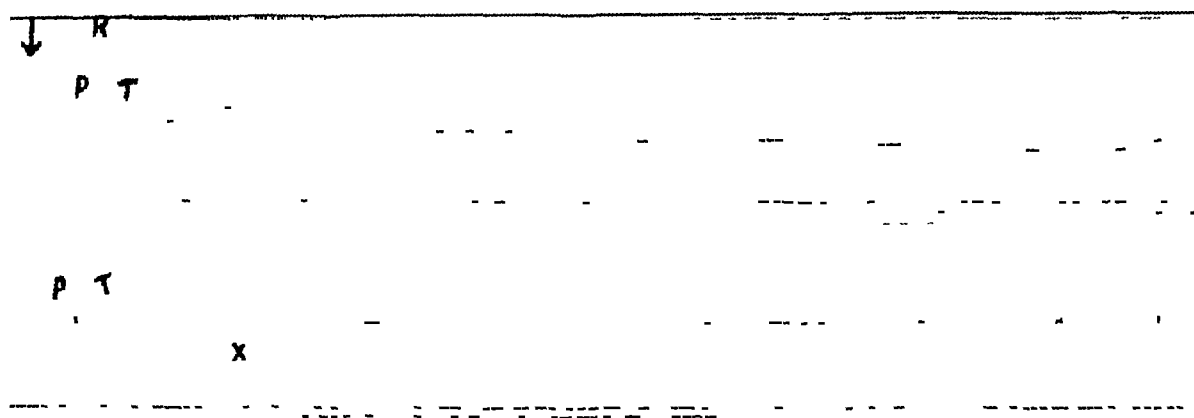


Fig 4 (patient E M) —A, the effect of pressure on the right carotid sinus, cardiac standstill of 10.4 seconds with the development of an Adams-Stokes seizure. B, after the administration of epinephrine, pressure on the right carotid sinus induces a nodal rhythm at X.

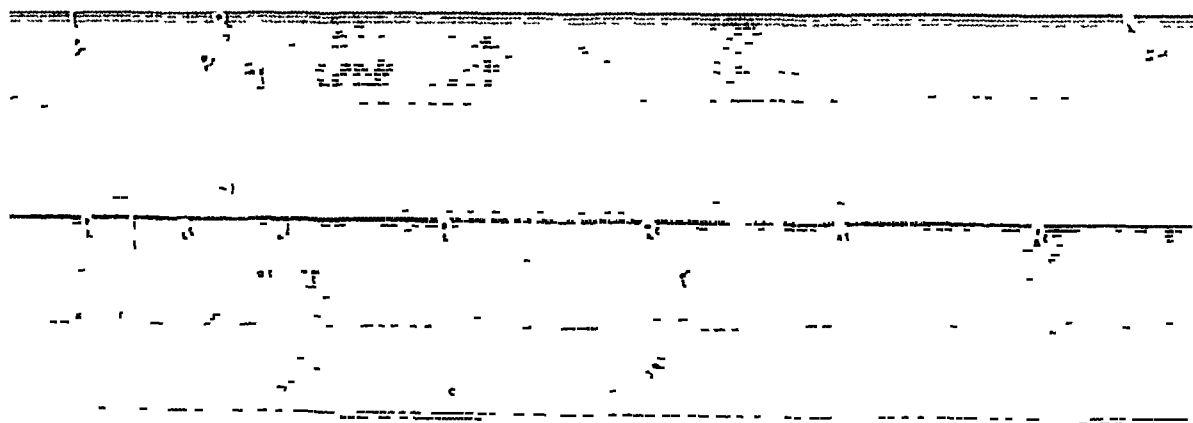


Fig 5 (patient J T) —A, a cardiac arrest of 82 seconds after right carotid sinus pressure. B, the effect of right carotid sinus pressure after the administration of epinephrine, with the onset of nodal rhythm shown at X.

muscle. This may be due in part to a direct effect on the muscle, since epinephrine increases the rate of a denervated heart, and in part to a stimulation of the accelerator nerves. Rothberger and Winterberg<sup>3</sup>

3 Rothberger, C J, and Winterberg, H. Ueber die experimentelle Erzeugung extrasystolischer ventrikulärer Tachykardie durch Acceleransreizung, Arch f d ges Physiol 142: 461, 1911.



found that ventricular rhythm could be produced by stimulation of the left sympathetic nerve if the right vagus was stimulated at the same time. Hering<sup>4</sup> destroyed the auriculoventricular bundle, and noted that the stimulation of the accelerators increased the rate of the ventricles. Cullis and Tribe<sup>5</sup> demonstrated that small doses of epinephrine increase the rate of auricles and ventricles both before and after section of the auriculoventricular bundle. Since 1916 there have been a number of clinical reports indicating that epinephrine has a favorable effect in preventing the Adams-Stokes seizures of heart block. The present experiments definitely indicate that epinephrine has a powerful effect on the impulse-initiating mechanism of the ventricles.

In the subject H. B. an attempt was made to study the duration of the effect of epinephrine. An electrocardiogram was taken, and pres-

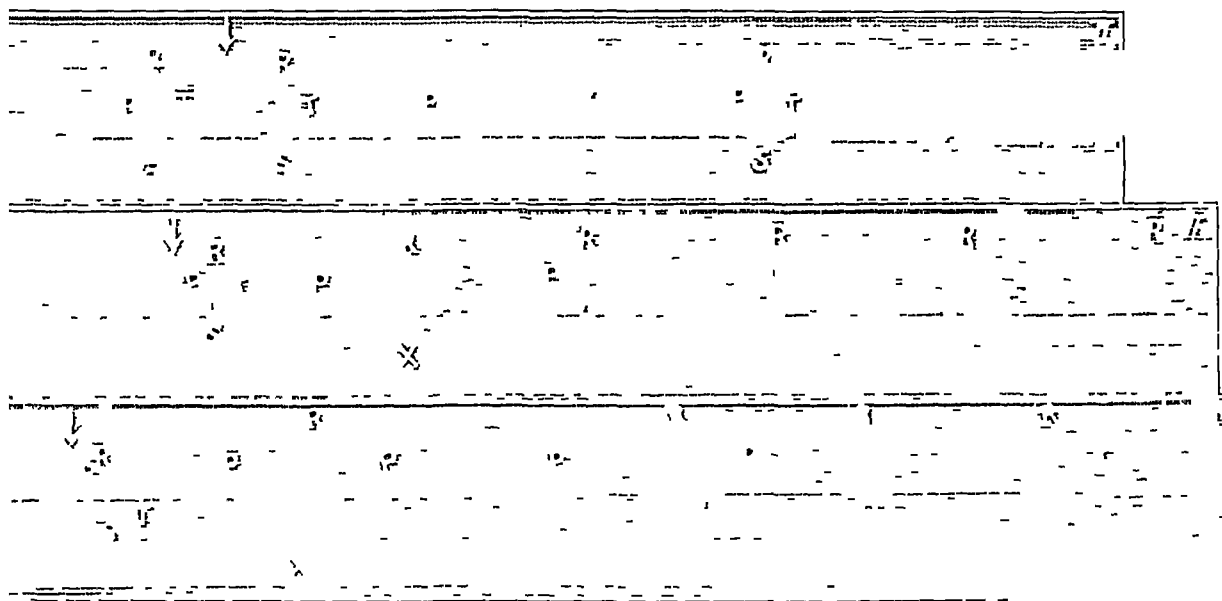


Fig. 6 (patient M. Y.)—A, lead 2, showing auriculoventricular block with ventricular standstill of 45 seconds after pressure on the right carotid sinus. B, lead 2, pressure on the right carotid sinus after the administration of epinephrine, with the onset of slow ventricular rhythm shown at X. C, lead 3, showing that the origin of the ectopic rhythm is in the left ventricle (new terminology).

sure on the right carotid sinus elicited in this instance a cardiac standstill of 82 seconds (fig. 7A). Fifteen minutes after the subcutaneous injection of 1.2 cc. of epinephrine hydrochloride, 1:1,000, pressure on the carotid sinus resulted in an idioventricular rhythm with a rate of 40 (fig. 7B). Thirty-five minutes after the injection of the drug a

4 Hering, H. E. Ueber die unmittelbare Wirkung des Accelerans und Vagus auf automatisch-schlagende Abschnitte des Säugetierherzen, *Arch. f. d. ges. Physiol.* **108** 281, 1905.

5 Cullis, W. E., and Tribe, E. M. Distribution of Nerves in the Heart, *J. Physiol.* **46** 141, 1913.

similar response was obtained with a somewhat more rapid ventricular rate. Fifty-five minutes after the injection of epinephrine hydrochloride, pressure on the right carotid sinus again induced a long cardiac arrest, lasting 9.5 seconds (fig 7 *D*). From this experiment it appeared that the effect of epinephrine passes off between thirty-five and fifty-five minutes after subcutaneous injection.

Luckhardt and Koppanyi<sup>6</sup> demonstrated in dogs that massage of the site of subcutaneously injected epinephrine hydrochloride may produce a pressor effect many hours after the injection. In the present experiment, the epinephrine was injected without massage of the area

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Fig 7 (patient H. B.) —The duration of the effect of epinephrine. *A*, cardiac standstill of 87 seconds after pressure on the right carotid sinus (at arrow), *B*, ventricular rhythm on right carotid pressure, fifteen minutes after the administration of epinephrine. *C*, ventricular rhythm on right carotid compression thirty-five minutes after epinephrine, *D*, cardiac standstill of 9.5 seconds induced by right carotid pressure fifty-five minutes after epinephrine.

of injection. After the effect of the epinephrine had passed off, the site of the injection was actively massaged. Ten minutes after this procedure, pressure on the carotid sinus again elicited a ventricular rhythm similar to that following the injection of epinephrine. Twenty minutes after the massage of the epinephrized area, a similar effect

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<sup>6</sup> Luckhardt, A. B., and Koppanyi, T. Studies on the Hemodynamic Action of Subcutaneously Injected Epinephrine, *Am J Physiol* **81** 436, 1927.

was obtained (fig 8). Further studies are in progress concerning the duration of the effect of epinephrine and the renewal of this effect by massage. From this experiment, however, it appears that subcutaneously injected epinephrine remains active, and that there is a return of the cardiac effect after massage of the site of injection.

*Ephedrine*—Ephedrine was used because of the similarity of many of its effects to those of epinephrine, and because it is frequently employed as a substitute for this drug. The effect of ephedrine was studied on two occasions on the subject H. B. In the first experiment, ephedrine sulphate was administered by mouth for four days in doses of 50 mg. four times a day. In addition 100 mg. of ephedrine hydrochloride was given subcutaneously one hour before the record was taken. Pressure on the right carotid sinus induced a cardiac standstill of 88 seconds (fig 9). The reaction differed in no way from the usual

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Fig 8 (patient H. B.)—Massage of the epinephrinized area one hour after subcutaneous injection. *A*, ten minutes after massage, ventricular rhythm rate 43 on right carotid pressure (at arrow). *B*, twenty minutes after massage, ventricular rhythm rate 38 on right carotid pressure (at arrow).

control record. After an interval of three weeks, the experiment was repeated after the subcutaneous injection of 100 mg. of ephedrine hydrochloride, with a similar result. It was apparent that in this patient ephedrine had no effect in increasing the ventricular excitability such as was clearly demonstrated with epinephrine. Certain observations suggest that ephedrine acts differently on the heart than does epinephrine. Gradinesco<sup>7</sup> found that epinephrine is able to restore the beat of the frog's heart which has been arrested by perfusion with ephedrine. Bain<sup>8</sup> perfused the hearts of crabs, and found that epinephrine in 1:50,000

<sup>7</sup> Gradinesco, A. Difference d'action entre l'éphedrine et l'adrénaline, *Compt rend Soc de biol* **96** 1027, 1927.

<sup>8</sup> Bain, W. A. Action of Adrenaline and of Certain Drugs on the Isolated Crustacean Heart, *Quart J Exper Physiol* **19** 297, 1929.

dilution caused a marked increase in the rate and tone of the heart, while ephedrine had no effect. La Barre<sup>9</sup> showed that ephedrine does not lead to ventricular fibrillation in cats under chloroform anesthesia, in which respect it differs from epinephrine. Wilson, Pilcher and Harrison<sup>10</sup> noted in dogs that both epinephrine and ephedrine usually increase the cardiac output, but that while epinephrine increases the heart rate ephedrine has the opposite effect. The effect on the human heart has been studied with variable results.<sup>11</sup> A slowing of the heart has been observed most frequently, but acceleration or absence of effect has also been noted. There are several clinical reports which suggest that ephedrine may be substituted for epinephrine in the treatment of the syncopal attacks of heart block. Miller<sup>11b</sup> reported an increase in auricular and ventricular rates following subcutaneous injections of ephedrine. Fahr,<sup>12</sup> Hollingsworth,<sup>13</sup> Stecher<sup>14</sup> and Wood<sup>15</sup> reported favorable results in the prevention of the Adams-Stokes seizures by the oral administration of the drug.



Fig 9 (patient H. B.)—Effect of ephedrine. Right carotid sinus pressure (at arrow) induced a cardiac standstill of 88 seconds after the oral administration of 200 mg and 100 mg subcutaneously daily for four days.

9 La Barre, J. Existe-t-il une syncope éphédrino-chloroformique, *Compt rend Soc de biol* **98** 863, 1928.

10 Wilson, C. P., Pilcher, C., and Harrison, T. R. The Effect of Drugs on Cardiac Output, Effect of Ephedrine on Minute Cardiac Output of Normal Dogs, *Arch Int Med* **41** 622 (May) 1928.

11 (a) Chen, K. K., and Schmidt, C. F. The Action of Ephedrine, the Active Principle of the Chinese Drug, Ma Huang, *J Pharmacol & Exper Therap* **24** 339, 1924. (b) Miller, T. G. A Consideration of the Clinical Value of Ephedrine, *Am J M Sc* **170** 157, 1925. (c) Rowntree, L. G., and Brown, G. E. Ephedrine Therapy in Addison's Disease, *Endocrinology* **10** 301, 1926. (d) Rudolph, R. D., and Graham, J. D. Notes on Sulphate of Ephedrine, *Am J M Sc* **173** 399, 1927. (e) Middleton, W. S., and Chen, K. K. Ephedrine, a Clinical Study, *Arch Int Med* **39** 385 (March) 1927.

12 Fahr, George. Personal communication.

13 Hollingsworth, M. Ephedrine in Adams-Stokes Syndrome, *California & West Med* **26** 802, 1927.

14 Stecher, R. M. A Note on Adams-Stokes Disease Treated with Ephedrine, *Am Heart J* **3** 567, 1928.

15 Wood, J. E., Jr. Ephedrine in Adams-Stokes Syndrome, *J A M A* **98** 1364 (April 16) 1932.

There was no evidence, however, in the present study that ephedrine increased the rhythmic property of the ventricular muscle sufficiently to initiate a ventricular rhythm. It is realized that no definite conclusions are justifiable, since the observations are limited to a single subject, and since it has already been noted that there is some variability

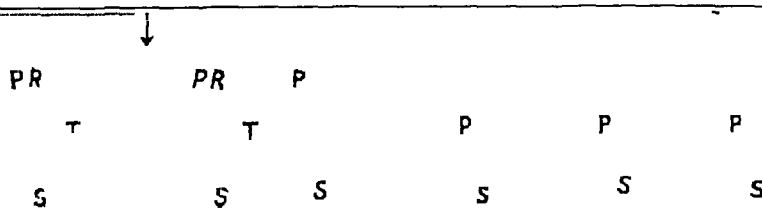


Fig 10 (patient H B) —Lead 3, the effect of the administration of barium chloride, 200 mg daily by mouth for four days. After right carotid sinus pressure (at arrow) there was a displacement of the pace-maker and a slowing of the heart from 60 to 40 beats a minute.

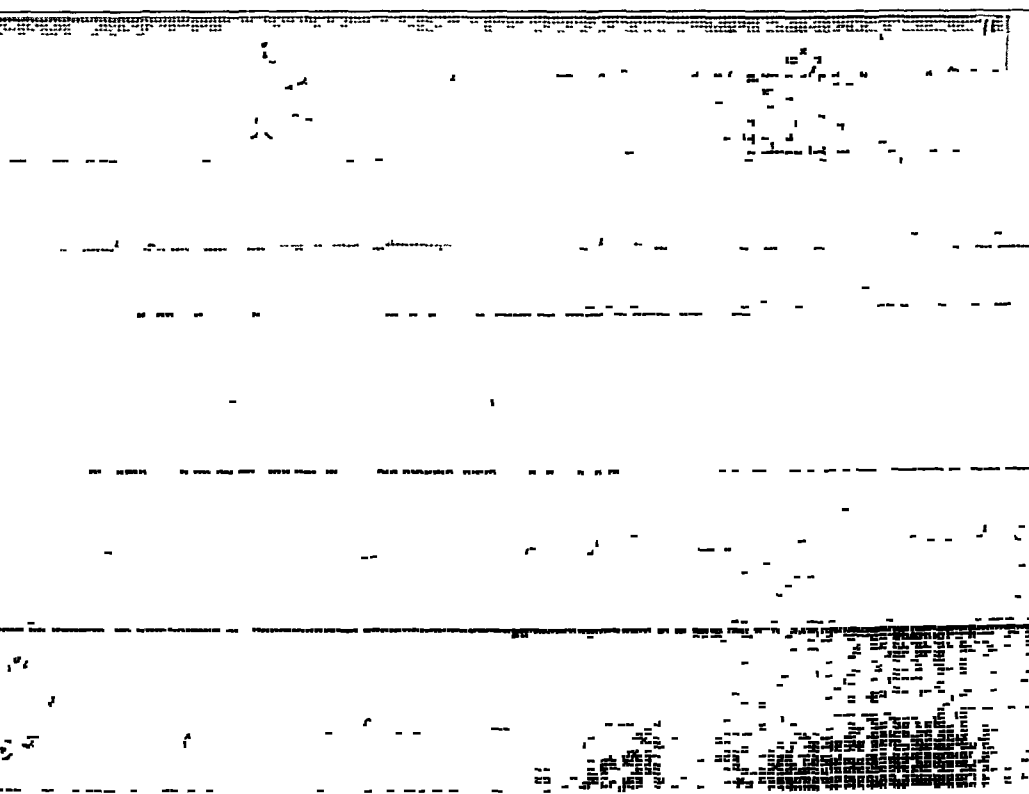


Fig 11 (patient J M) —Effect of barium chloride, 250 mg a day for three days. A, before carotid sinus pressure. B and C are a continuous record, showing a cardiac arrest of 11.6 seconds after right carotid sinus compression (at arrow). D, after the administration of barium chloride without carotid pressure. E, right carotid compression (at arrow) after barium chloride showing the development of a slow idioventricular rhythm.

in the effect of ephedrine on the human heart. A study of a larger group of subjects is in progress and will be reported on later. It is

significant, however, that ephedrine failed to have any effect in a person who responded readily to epinephrine

*Barium Chloride*—The effect of barium chloride was studied in two subjects. In the subject H. B., the drug was administered in doses of 50 mg four times a day. Figure 10 demonstrates that the prolonged cardiac standstill following pressure on the carotid sinus was abolished. The heart rate was slowed from 60 to 40 beats a minute, and the P wave became inverted, indicating the development of a new pacemaker in the auricle. In the second subject, J. M., barium chloride was administered in doses of 250 mg daily for three days. The strips B and C in figure 11 form a continuous record showing the effect of pressure on the right carotid sinus prior to the administration of the drug. After a slowing of the heart, there was a period of cardiac standstill of 11.6 seconds, which terminated in a typical Adams-Stokes seizure. The oscillations that appear at the end of the string in strip C are due to convulsive movements of the patient's extremities. Figure 11 E is a repetition of carotid sinus pressure after the administration of the barium chloride. A series of aberrant ventricular complexes appear indicating the development of an idioventricular rhythm, the rate varying from 30 to 40 beats a minute.

Various experimental studies indicate that barium chloride increases the excitability curve of the ventricles when given in sufficiently large doses. Rothberger and Winterberg<sup>3</sup> observed that after intravenous injection of from 5 to 10 mg of barium chloride, the heart cannot be arrested by simultaneous stimulation of the sympathetic and vagus nerves, as is the case in the normal heart. With small doses of barium chloride, ectopic ventricular rhythms could regularly be produced by stimulation of the sympathetic nerves. With larger doses, various types of ventricular rhythms occurred spontaneously to the point of ventricular fibrillation. The auricles were affected to a lesser degree than the ventricles. Von Egmond<sup>16</sup> studied the effects of various drugs in experimental heart block. He demonstrated that the ability of the ventricles to initiate rhythms was distinctly increased by barium chloride. After repeated injections of the drug, ventricular fibrillation usually followed. Many patients with clinical cases of heart block have been treated with barium chloride. It has been observed that the drug exerted a beneficial effect in some cases, while in others it apparently was of no value. This treatment was first used by Wilson and Hermann<sup>17</sup> at the suggestion of Dr. S. A. Levine. In this case, there was no effect on the frequency of the Adams-Stokes seizures. Cohn and

16 von Egmond, A. A. J. Ueber die Wirkung einiger Arzneimittel beim vollständigen Herzblock, *Arch f d ges Physiol* **154** 39, 1913.

17 Wilson, F. N. and Hermann, G. R. Some Unusual Disturbances of the Mechanism of the Heart Beat *Arch Int Med* **31** 923 (June) 1923.

Levine,<sup>18</sup> however, have reported beneficial effects from the use of this drug. Paisonnet and Hyman<sup>19</sup> found barium chloride of no value in the treatment of eight patients with heart block. It appears from the present study that barium chloride may in some instances affect the auricles and have little influence on the ventricular muscle, as in the subject H. B. Such an effect would be of no benefit in complete heart block. The subject J. M., however, offers a clear demonstration that barium chloride can increase the ability of the ventricles to initiate a rhythm and thus prevent a cardiac standstill. Following this experiment, the patient H. B. received a subcutaneous injection of epinephrine hydrochloride, 1:1,000. Fifteen minutes later, pressure on the right carotid sinus elicited an idioventricular rhythm similar to that induced in the previous experiments with epinephrine. This indicates that the ventricular muscle at this time was susceptible to the initiation of a rhythm if a sufficiently active drug was introduced.

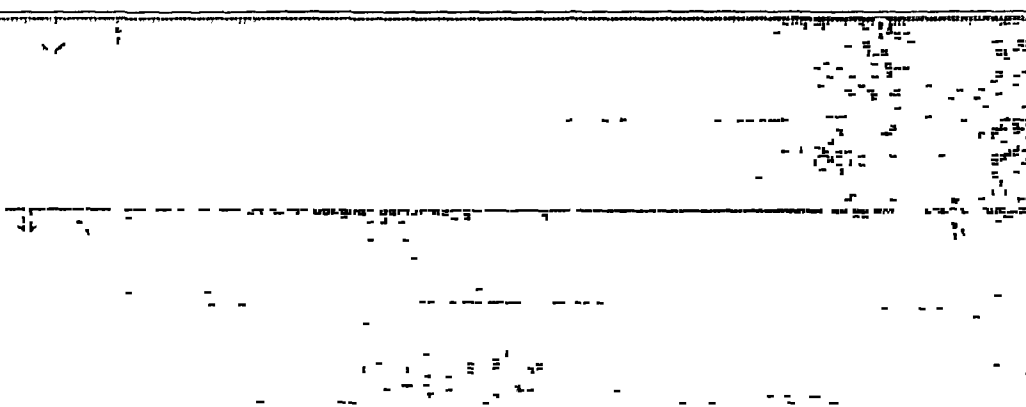


Fig. 12 (patient H. B.)—A, cardiac standstill of seven seconds after pressure on the right carotid sinus. B, repetition of the pressure twenty minutes after the intravenous injection of 15 cc of 10 per cent calcium gluconate, with a cardiac arrest of 8 seconds.

*Calcium Gluconate*—The effect of calcium gluconate was studied in the subject H. B. on two occasions. Figure 12 shows the effect of an intravenous injection of 15 cc of a 10 per cent solution. It was apparent from this experiment that the administration of calcium did not raise the rhythmicity of the ventricles sufficiently to initiate a ventricular rhythm during the period of cardiac standstill. Calcium gluconate was then given by mouth in doses of 4 Gm. four times a day for a week. A repetition of the pressure on the carotid sinus again demonstrated that the drug was ineffective. Rothberger and Winterberg.<sup>3</sup>

18 Cohn, A. E., and Levine, S. A. The Beneficial Effects of Barium Chloride on Adams-Stokes Disease, *Arch Int Med* **36**: 1 (July) 1925.

19 Parsonnet, A. E., and Hyman, A. S. Barium Chloride in Stokes-Adams Syndrome of Complete Heart Block, *Am J M Sc* **180**: 356, 1930.

concluded that the action of calcium on the rhythmic property of the ventricles was similar to that of barium, but that larger doses were necessary. They noted, however, that with calcium, stimulation of the vagus without stimulation of the accelerators caused a longer cardiac standstill than before the administration of the calcium. These observers consider that the action of barium and calcium is to cause the impulse-initiating mechanism in the ventricles to be more favorably influenced by stimulation of the accelerators. It would seem that the failure of barium and calcium to affect the ventricles in the patient H. B. might be explained by the presence of a low tone of the accelerators. If the response to epinephrine is to be considered as an indication of the degree of accelerator activity, the minimal reaction in this patient supports such a conception. It is also possible that a low tone of the accelerators may explain the cases in which complete heart block was unsuccessfully treated with barium chloride.

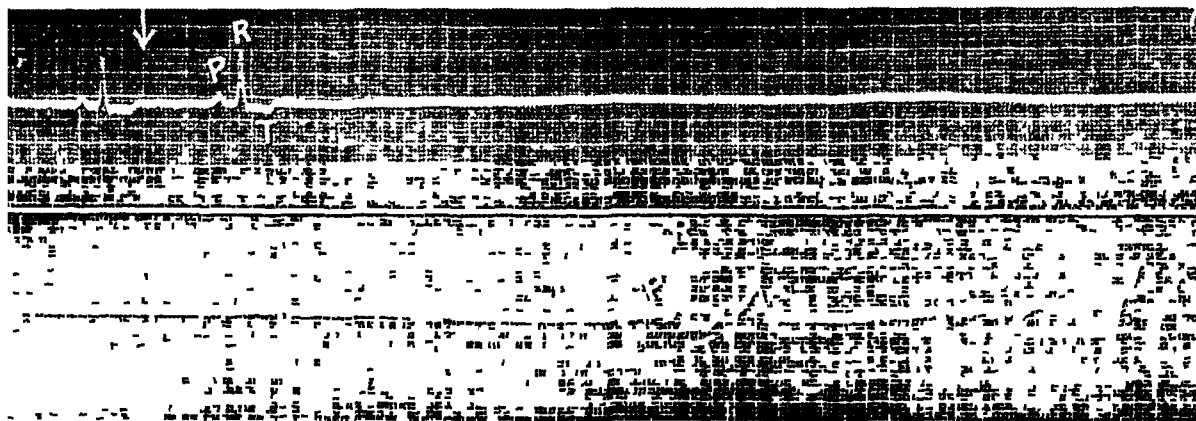


Fig 13 (patient H. B.)—Effect of digitalis, 3 grains (0.195 Gm.) daily for a week. A and B form a continuous record showing cardiac standstill of 15.4 seconds after right carotid sinus pressure (at arrow)

*Digitalis*—The patient H. B. received 0.2 Gm. of the powdered leaf daily for seven days before the first observations were made. It should be repeated here that in the control studies the longest period of cardiac standstill induced was 9 seconds, and on no occasion was there a period of cardiac arrest of sufficient duration to result in convulsions or syncope. Figure 13 shows the reaction to pressure on the right carotid sinus after the administration of 1.4 Gm. of digitalis in a week. The duration of the cardiac standstill is 15.4 seconds, at which time a typical Adams-Stokes syncope occurred. During the following two weeks, the powdered leaf was administered in doses of 0.12 Gm. a day. During this period a number of observations were made, and the period of cardiac standstill was consistently prolonged as compared with the control records. There was no evidence of idioventricular beats during the period of cardiac arrest in any of the records. It is clear that following



the administration of digitalis there is an exaggeration of the cardiac inhibition induced by pressure on the carotid sinus. The prolongation of the period of cardiac arrest may be explained as a summation of two similar effects: a reflex stimulation of the vagus by the carotid pressure and a stimulation of the vagus by digitalis. Wenckebach<sup>20</sup> stated that digitalis increases the effect of vagus stimulation on the heart. Hering<sup>2</sup> noted in dogs that digitalis intensified the cardiac portion of the carotid sinus reflex. The absence of any tendency to ectopic rhythm may be explained by incomplete digitalization. Rothberger and Winterberg<sup>21</sup> found that strophanthin had a definite influence on ventricular rhythmicity only in toxic doses. Robinson and Wilson<sup>22</sup> observed that while 25 per cent of a fatal dose produced alterations in the T wave and 50 per cent a definite change in the P-R interval, ectopic beats were not elicited until 75 per cent of the lethal dose was used. Gold and his

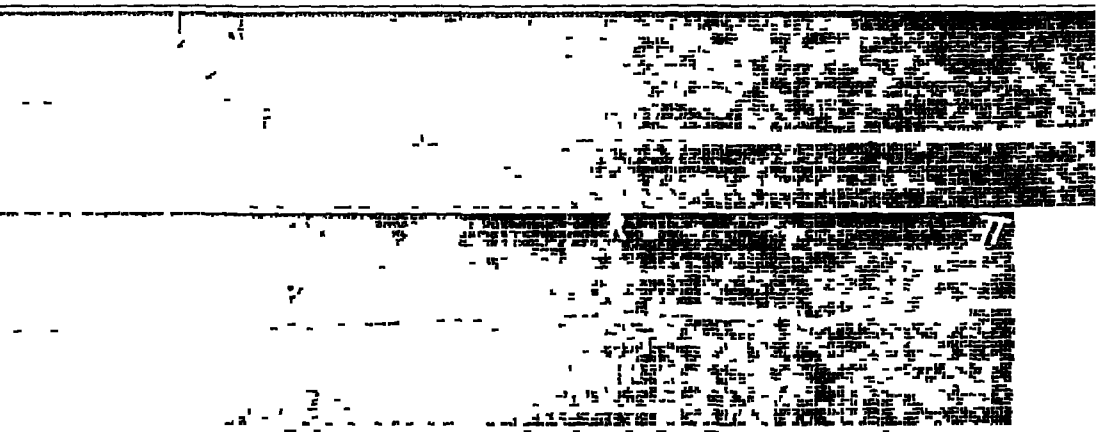


Fig 14 (patient H. B.)—A and B form a continuous record showing effect of right carotid sinus pressure (at arrow) after administration of 0.7 Gm of caffeine sodio-benzoate intravenously, with a cardiac arrest of 144 seconds. The patient was partially digitalized at the time of this experiment.

associates,<sup>23</sup> however, noted that prolongation of the P-R interval and appearance of ectopic beats occurred in approximately the same dosage in unanesthetized cats. From the present observation it appears that digitalis may distinctly increase the effect of vagus stimulation on the heart in a dosage below that which will induce ectopic ventricular beats.

20 Wenckebach, K. F. The Effects of Digitalis on the Human Heart, *Brit M J* **2** 1600, 1910.

21 Rothberger, C. J., and Winterberg, H. Ueber die Einfluss von Strophanthin auf die Reizbildungsfähigkeit der automatischen Zentren des Herzens, *Arch f d ges Physiol* **150** 217, 1913.

22 Robinson, G. C., and Wilson, F. N. A Quantitative Study of the Effects of Digitalis on the Heart of the Cat, *J Pharmacol & Exper Therap* **10** 491, 1918.

23 Gold, H., Hitzig, W., Gelfand, B., and Glassman, H. A Qualitative Comparison of Various Digitalis Bodies, *Am Heart J* **6** 237, 1930.

The effect of atropine sulphate was observed when the patient was partially digitalized. A cardiac arrest of 15 seconds induced by right carotid sinus pressure was completely abolished by the subcutaneous injection of 2 mg of atropine sulphate.

*Caffeine*—The effect of the administration of caffeine is illustrated in figure 14. The subject was partially digitalized at the time of this experiment, and a cardiac arrest of from 14 to 16 seconds could be easily obtained. Electrocardiograms were taken at various intervals following the administration of the drug. Figure 14 is a typical record taken ten minutes after the intravenous injection of 0.7 Gm of caffeine sodio-benzoate. Pressure on the right carotid sinus elicited a ventricular standstill of 14.4 seconds interrupted by only one auricular contraction. There is some difference of opinion as to the effect of caffeine on the rhythmic function of the heart muscle. Von Egmond<sup>16</sup> observed in experimental heart block that caffeine caused a transient increase in the rate of ventricular contractions. He obtained this effect, however, only with amounts of the drug far above the ordinary therapeutic dose. Sollmann<sup>24</sup> stated that in experimental heart block caffeine given experimentally in moderate doses increases the rate of the heart, and that large doses may produce ventricular extrasystoles and tachycardia. According to Hirschfelder,<sup>25</sup> however, caffeine has no effect on the duration of ventricular stoppage, as it has been used without effect in cases of Adams-Stokes syncope. The results of this experiment indicate that caffeine in therapeutic doses does not increase cardiac rhythmicity sufficiently for the development of new centers of impulse initiation when the heart is deprived of its normal pacemaker.

#### COMMENT

There have been many studies concerned with the effect of drugs on the rhythmic property of the heart muscle. This problem is of practical importance since sudden cardiac standstill usually occurs because the heart for a time has lost the mechanism for initiating the stimulus required for its activity. This is frequently the condition underlying the cardiac arrest under anesthesia, in shock, in asphyxia of the new-born or of premature infants and in the ventricular asystole of complete heart block. Previous observations have consisted chiefly of studies in experimental animals both on the normally beating heart and on experimental heart block. The studies on the human heart include reports on the effect of drugs in the prevention of the syncopal

<sup>24</sup> Sollmann, T. A Manual of Pharmacology, ed 4, Philadelphia, W. B. Saunders Company, 1932, p. 280.

<sup>25</sup> Hirschfelder, A. D. Diseases of the Heart and Aorta, ed 3, Philadelphia, J. B. Lippincott Company, 1918, p. 587.

attacks of heart block and on the methods of resuscitation of the stopped heart by intracardiac therapy. From the various observations there has been no general agreement as to the efficiency of drugs in the prevention and treatment of cardiac standstill. The method of cardiac arrest induced by pressure on the carotid sinus permits a direct and well controlled study of the action of the drugs on the rhythmic property of the human heart muscle. It is recognized that the comparatively small number of observations does not permit a final conclusion as to the exact efficiency of the various drugs used. The fact that epinephrine, when repeatedly used in one subject and in four others, consistently abolished the cardiac standstill by initiating an idioventricular rhythm strongly indicates that this drug exerts a powerful effect on the rhythmic property of the ventricular muscle. The study of a larger group of suitable subjects is in progress in order to evaluate more accurately the efficiency of various drugs and also to bring out certain features of their action, such as the duration of the effect and the influence of the mode of administration.

#### SUMMARY

- 1 The prolonged cardiac standstill induced by pressure on the carotid sinus was utilized as the basis for the study of the effect of drugs on the rhythmic function of the human heart.

- 2 The exaggerated carotid sinus reflex in man could be abolished by atropine.

- 3 Epinephrine had a powerful effect on the impulse-initiating mechanism of the ventricles and consistently prevented cardiac standstill by the induction of an idioventricular rhythm.

- 4 The stimulation of cardiac rhythmicity by the administration of epinephrine passed off within an hour after a subcutaneous injection. The effect returned after massage of the site of injection.

- 5 Ephedrine had no effect in a patient who repeatedly responded to epinephrine with initiation of a ventricular rhythm.

- 6 Barium chloride abolished cardiac arrest in one case by the formation of a new center in the auricles and in another instance by the development of an idioventricular rhythm.

- 7 Calcium gluconate had no influence on the cardiac standstill.

- 8 Digitalis definitely prolonged the period of cardiac standstill induced by pressure on the carotid sinus. This effect was abolished by atropine.

- 9 Caffeine in a therapeutic dose had no effect on the duration of the cardiac arrest.

# HYPERPLASTIC SCLEROSIS OF THE PULMONARY ARTERY AND ARTERIOLES

REPORT OF A CASE WITH DISCUSSION OF THE PATHOGENESIS

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Sclerosis of the pulmonary artery and arterioles associated with Ayerza's syndrome occurs secondary to a variety of diseases, congenital and acquired, of the heart, lungs, pericardium, pleura and blood vessels (Miller<sup>1</sup>). Primary sclerosis developing independently of these conditions is much less frequent. The majority of the latter cases are due to syphilis (Rogers,<sup>2</sup> Warthin,<sup>3</sup> Arrillaga,<sup>4</sup> Elizalda,<sup>5</sup> Hare and Ross,<sup>6</sup> Thomas,<sup>7</sup> Bruce and co-workers,<sup>8</sup> Cheney,<sup>9</sup> Weber and Bode<sup>10</sup> and Konstam and Turnbull<sup>11</sup>), a few to rheumatic fever (Paul<sup>12</sup>). In a smaller group the lesion is hyperplastic and noninflammatory and the etiology obscure (Rosenthal,<sup>13</sup> Bacon and Apfelbach<sup>14</sup>).

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From the Department of Diseases of the Chest and the Pathological Laboratories of the Jefferson Medical College and Hospital

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## REPORT OF CASE

G P, a stevedore, white, aged 48, was first seen in October, 1924, complaining of a cough productive of a small amount of mucus, a feeling of constriction across the upper part of the chest and dyspnea, which had developed over a period of five years. The family history was irrelevant. His wife had had five children, all living and well, and had had no miscarriages. He had typhoid fever in 1906 and influenza and pneumonia in 1918, he denied having had gonorrhea or syphilis.

He was obese, dyspneic and cyanotic. There was no clubbing of the fingers or curving of the nails, and the radial arteries were not thickened. The chest was barrel-shaped, expansion limited and vocal fremitus normal. The percussion note was hyperresonant, and musical râles obscured the breath sounds. The apex beat was not visible or palpable, the area of cardiac dullness was diminished, sounds were distant and regular and there were no murmurs. There was a marked accentuation of the pulmonic second sound. The liver was not enlarged and the spleen was not palpable. Blood pressure was 145 systolic and 98 diastolic.

No tubercle bacilli, Curschmann's spirals or Charcot-Leyden crystals were found in the sputum. The urine contained a faint trace of albumin but no casts. Repeated Wassermann and Kahn tests of the blood were negative. The hemoglobin content was 85 per cent, the erythrocytes ranged between 4,300,000 and 5,200,000, the leukocytes numbered 10,880, of which 66 per cent were polymorphonuclears, 29 per cent lymphocytes and 4 per cent eosinophils. Blood sugar amounted to 116 mg, calcium to 11.5 mg and phosphorus to 3.6 mg.

On bronchoscopic examination the bronchial mucosa was congested and covered with adherent tenacious mucopurulent material.

Roentgen examination of the chest showed the root markings increased in density. The heart was slightly enlarged to the right, and there was some increase in the shadow in the region of the arch of the pulmonary artery. The left seventh rib showed an old fracture.

Electrocardiographic study on April 21, 1927, showed cardiac rate, 105 per minute, rhythm regular, conduction function normal, no disturbance of muscle balance, and no indications of myocardial degeneration.

During the period of observation from 1924 until the patient's death, dyspnea, cyanosis and a brassy cough were continuously present. On two occasions death appeared imminent. Early in 1925, paroxysmal dyspneic attacks, simulating asthma, developed, these usually occurred at night frequently as often as five times a week, and were only occasionally relieved by epinephrine. On testing for susceptibility to proteins a severe reaction was obtained with dog and rabbit hair. Attempts to desensitize the patient resulted in no improvement. His condition remained unchanged until February, 1930, when an acute respiratory infection precipitated a sudden exacerbation accompanied by a small pulmonary hemorrhage. In June, 1931, he became bedfast on account of weakness and headaches, which were constant, severe and greatly aggravated by coughing. The dyspnea became intense and was present even during sleep. Edema appeared, and involved chiefly the chest, abdomen and external genitalia. The cyanosis deepened, causing a decided change in the patient's appearance. Beginning as a ring around the neck at the lower border of the thyroid cartilage, it extended upward over the face and head, and was also marked beneath the finger and toe nails. During sleep and following paroxysms of coughing the face turned black. In July the asthmatic attacks and the feeling of thoracic constriction disappeared. The pain was now localized, constant and aggravated by coughing. In the latter part of November the patient became drowsy, edema and cyanosis increased, the headache and precordial pain disap-

peared The temperature remained below 99.2 F, the pulse rate between 92 and 110 Death occurred in stupor on Dec 15, 1931

It was apparent that chronic bronchitis, emphysema and bronchial asthma were present It did not appear that these were enough to cause so severe a grade of cyanosis or such distressing constant dyspnea The symptoms resembled more those due to increased pressure within the chest The possibility of a new growth, aneurysm, enlarged bronchial nodes or a persistent thymus was considered Lack of definite physical signs and negative roentgenographic, bronchoscopic and laboratory evidence eliminated these With the development of edema and the typical appearance of the "black cardiac" during the last few months of life, it became increasingly evident that the heretofore unexplained symptoms were due to sclerosis of the pulmonary artery

*Postmortem Examination*—This was conducted two hours after death Edema was generalized and especially marked on the trunk, scrotum and penis There were deep cyanosis and scattered petechiae of the face and extremities The peritoneal cavity contained 6,000 cc, the left pleural cavity 800 cc, the right pleural cavity 300 cc and the pericardium 200 cc of a thin, clear transparent fluid

The heart was hypertrophied and dilated, and weighed 530 Gm The apex was formed by the right ventricle, the wall of which was 10 cm thick The columnae carnae and papillary muscles were hypertrophied and flattened The valve rings were dilated and the endocardium normal The myocardium, aorta and coronary arteries were normal except that the right coronary was dilated

Anteriorly both lungs were crepitant, voluminous, dry, light brown, resistant to compression and partially collapsed posteriorly The bronchi were contracted and thickened The first portion of the pulmonary artery was dilated, and in its main branches were a few flat, grayish-yellow, firm plaques, which became more numerous with each succeeding branch

The spleen was enlarged, congested and fibrotic

The liver was dark red, shrunken firm, tough and slightly nodular, and cut with increased resistance

Both kidneys were congested The suprarenals were swollen, bright yellow and well preserved

The stomach and upper portion of the small intestine were congested, the mucosa was necrotic and the lumen contained coffee-ground material

The lymph nodes about the aorta were dark red, swollen and soft

The bone marrow in the ribs, vertebrae and sternum was bright red There was an osseous irregularity of the seventh left rib at the sternal border, which had the appearance of an old fracture and caused compression of the intercostal tissues

The anatomic diagnosis was sclerosis of the pulmonary artery, hypertrophy and dilatation of the right side of the heart, emphysema of the lungs, passive congestion of the liver, spleen, lymph nodes, kidneys, suprarenals, stomach and intestine, petechial hemorrhages of the skin, anasarca, and hyperplasia of the bone marrow

*Microscopic Examination*—Sections were fixed in Zenker's fluid and a diluted solution of formaldehyde, USP (1:10), blocked in paraffin and stained with hematoxylin-eosin, Mallory's and van Gieson's connective tissue stains, Verhoeff's elastic tissue stain, Levaditi's method for demonstrating spirochetes in sections, and Gram's stain for bacteria in tissues

*Pulmonary Artery* The adventitia was normal The wall of the vessel was generally widened by an increase in the size and number of elastic fibers The intima showed mild generalized hyperplastic thickening, amounting in places to flat, slightly elevated plaques, which consisted of cellular connective tissue and frayed

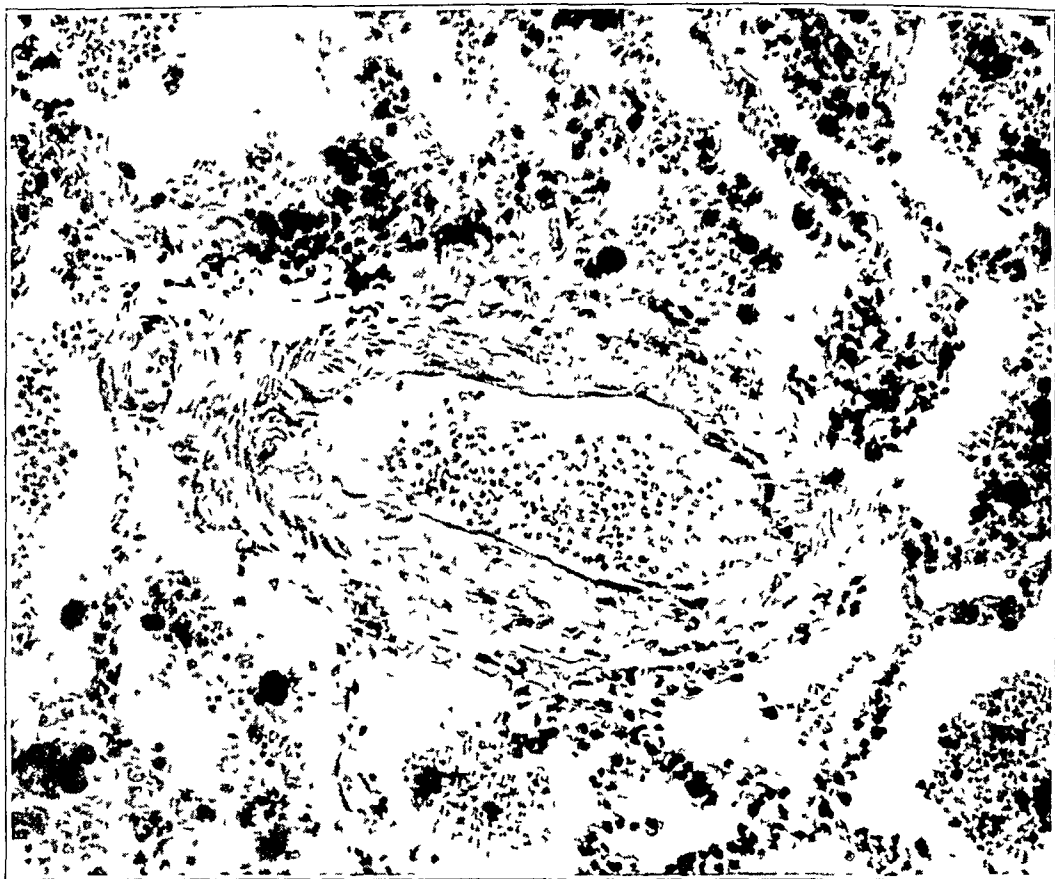


Fig 1—Lung an artery and to the left of it a small arteriole showing sclerotic process There are congestion of capillaries in the septums, hemorrhage and "heart failure" cells in the alveoli,  $\times 170$

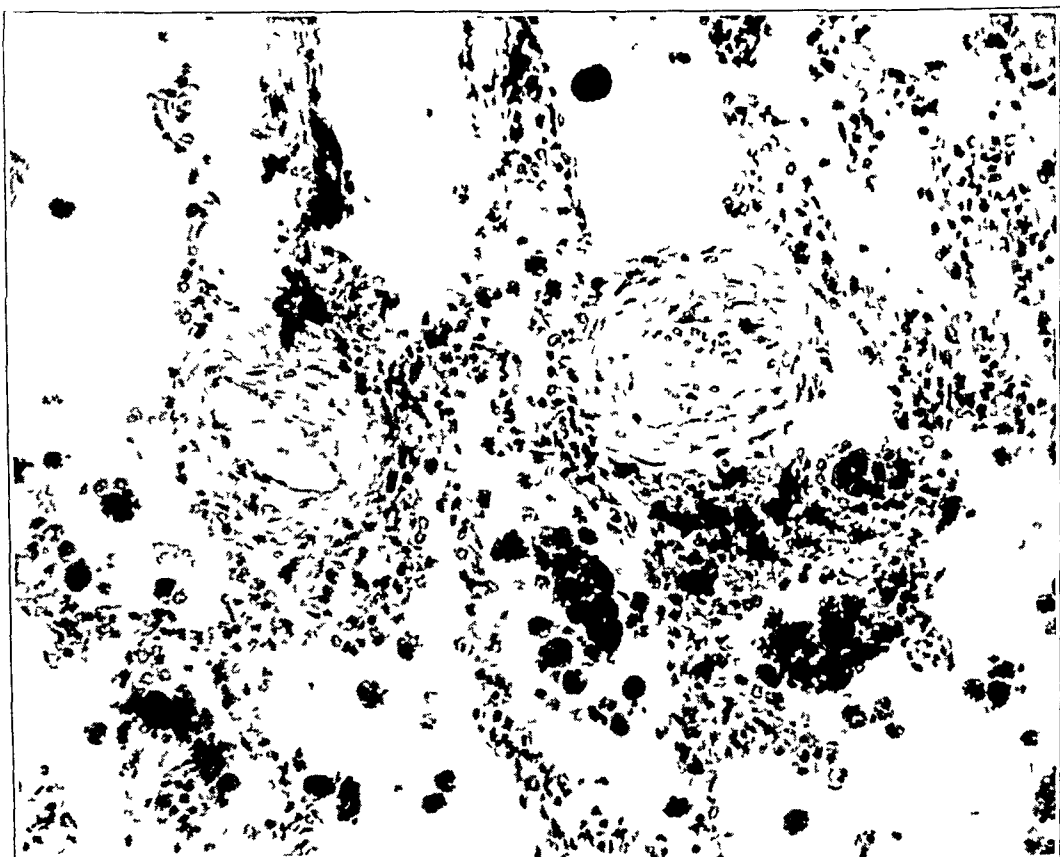


Fig 2—Lung two small arteries with thickened walls Many "heart failure" cells are present in the alveoli,  $\times 190$

elastic fibers. As the artery branched these changes gradually became more marked and differed in character. The intrapulmonary branches measuring from about 0.4 to 1 mm (figs 1 and 2) were greatly thickened and their lumens correspondingly narrowed. The thickening was chiefly the result of changes in the media and intima. The medial changes were an increase in muscle cells, elastic fibers and connective tissue. The intimal changes were a hyperplastic increase in connective tissue, hypertrophy, longitudinal splitting and fraying of the internal elastic lamina (fig 3). Variations of this consisted in great intimal thickening, atrophy of the adventitia and media and fusion of the internal and external laminae. Occa-



Fig 3—Lung: two small arteries in which there is splitting, fraying and reduplication of the elastica. Verhoeff's elastic tissue stain,  $\times 170$ .

sionally obstruction to the lumen resulted from nodular hypertrophy of the media. These changes became more accentuated with the branching of the arteries, those about 0.2 mm in diameter and smaller were completely occluded and all the rest greatly diminished. The process was much simpler and consisted of a subendothelial fibrosis in which elastic fibers were not so numerous or so large as in the medium-sized vessels (fig 1). The media was unchanged or but slightly atrophied. In none of the arteries were there any fresh thrombi. The vasa vasorum in all were dilated but otherwise unchanged. In none of them were there any round cell infiltrations. An occasional vacuolated space was noted in the media. The walls of the pulmonary capillaries were distinctly thickened. The pulmonary veins were normal except for one or two instances, in which thickening was slight. No bacteria were demonstrated.



**Lungs** Great numbers of polyblasts loaded with golden yellow and brownish pigment granules were present in the alveolar spaces. There was no edema, but in scattered patches gross hemorrhage was present (figs 1 and 2). Areas of partial collapse and emphysema were encountered, but neither was a striking feature. The alveolar walls were thickened by hyperemic capillaries and an appreciable increase of cellular and hyalinized connective tissue. They contained what small quantities of carbon deposit were present. In many the elastic fibers were apparently increased, but serial sections showed that this was mainly an artefact, most of the fibers belonging to the walls of arteries.

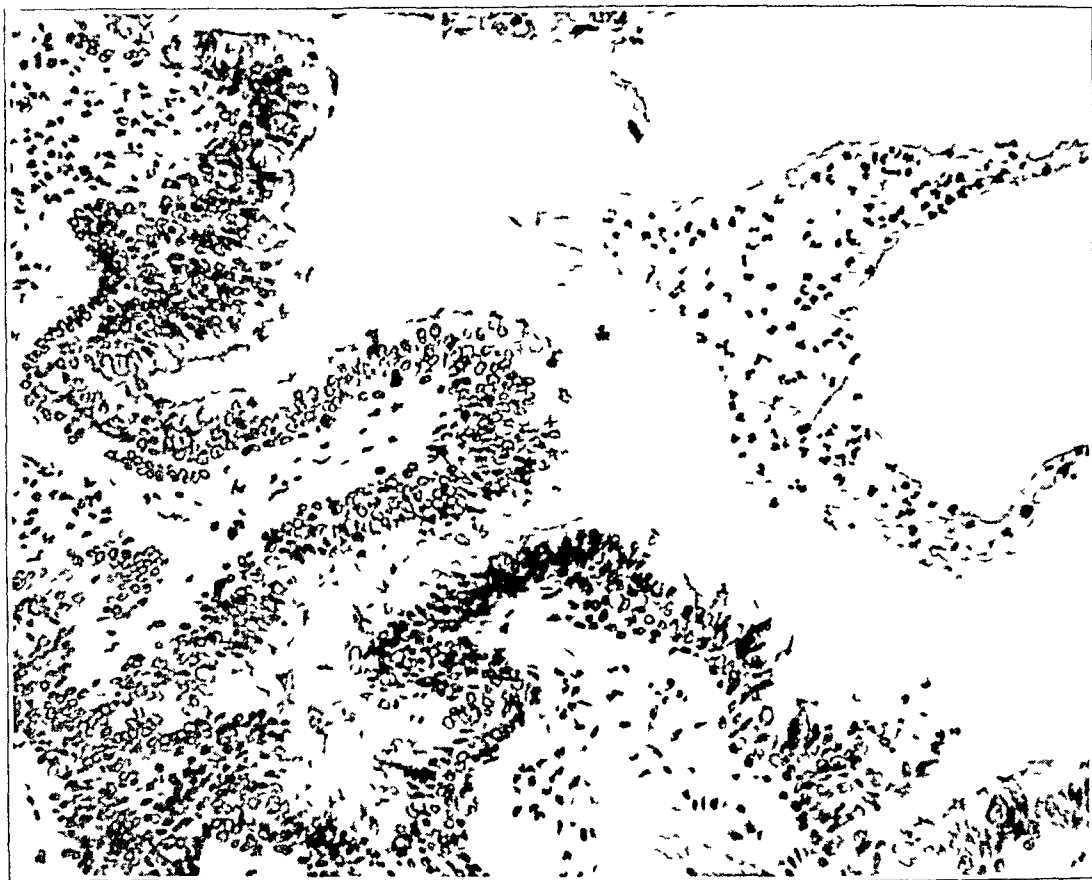


Fig 4—Bronchus. In the lumen there is a small amount of mucus in which eosinophils and neutrophils are caught. Folding of the mucosa and proliferation of bronchial epithelium can be seen. There is a slight infiltration of cells in the bronchial wall,  $\times 125$ .

The fibrous and muscular coats of the bronchi were slightly thickened. Their walls were sparsely infiltrated by eosinophilic and neutrophilic granulocytes. The vessels were hyperemic, but their walls were unchanged. The mucosa was thrown into folds and the lining cells proliferated to form in places from five to eight layers (fig 4). The lumens of many bronchi were narrowed and contained a small amount of stringy mucus, in the meshes of which were entangled desquamated epithelial cells, eosinophilic and neutrophilic granulocytes.

The arteries of the heart, kidney, spleen, liver and suprarenals were normal. In the liver about the portal radicals there was an active fibrosis with lymphocytes.

and proliferating bile ducts. It was of the nature of portal cirrhosis, but was not extensive enough to be so classed.

In the suprarenals the cells of the zona glomerulosa and medulla stained darkly. They were remarkably well preserved. Those of the zona fasciculata were more foamy than usual, owing to a large amount of lipoid.

In other respects the microscopic examination confirmed the gross findings.

#### COMMENT

The patient was under close clinical observation for seven years. As an etiologic factor syphilis was as well ruled out as possible. The history was not significant. The patient had no scars on the penis, and he had never had antisyphilitic treatment. The Wassermann and Kahn reactions of the blood were negative. The patient's wife had had five children and no miscarriages. All the children were living and healthy, and none showed any stigma of hereditary syphilis. There were no suggestive clinical manifestations, and roentgen studies of the patient's skeleton revealed no syphilitic lesions. After death no gross or microscopic evidences of the disease were found in the tissues. No spirochetes could be demonstrated, although diligently searched for. In the sections of the pulmonary arteries and arterioles there were no newly formed capillaries, round cell infiltrations in the adventitia and media or proliferative endarteritis of the vasa vasorum, characteristic of syphilitic arteritis.

Rosenthal's<sup>13</sup> cases of sclerosis of the pulmonary artery and arterioles were associated with constant aspiration of particulate matter (sand, iron) or fumes (naphtha, benzene), which he believed led to spasm and necrosis of capillary endothelium. Bacon and Apfelbach<sup>14</sup> regarded influenza as playing an important etiologic rôle. They reviewed some studies made on influenza during the acute attack in which necrosis of the capillary endothelium was observed. It is interesting that in our case symptoms appeared one year after an attack of influenzal pneumonia. McCann and Stephens<sup>15</sup> suggested rheumatic fever, but the changes in the arteries are not similar to those described for human beings (Pappenheimer and Von Glahn<sup>16</sup>) or for animals (Moon and Stewart<sup>17</sup>).

The present case suggests one of two other pathogenic factors. The first is endocrine. Over a long period of time this patient received injections of epinephrine hydrochloride. At autopsy the suprarenal cells were remarkably well preserved and were found to have a high

15 McCann, William S., and Stephens, D. J. *Tr. Am. Climat. & Clin. A.* **47** 3, 1931.

16 Pappenheimer, A. M., and Von Glahn, W. C. *Am. J. Path.* **2** 15, 1926.

17 Moon, V. H., and Stewart, H. L. *Experimental Rheumatic Lesions in Dogs and in Rabbits*, *Arch. Path.* **11** 190 (Feb.) 1931.

content of lipid (Cheney<sup>9</sup>) It has been shown that similar hyperadrenalinization of animals is followed by analogous lesions (Shaw,<sup>18</sup> Pearce<sup>19</sup> and Palentini<sup>20</sup>) Its effect is probably manifested by increasing resistance to blood flow, which Moschowitz<sup>21</sup> believes is of such great importance in causing arteriosclerosis

The second factor is neurologic There was an irregularity of the seventh left rib at the costosternal junction which diminished the intercostal space and pressed on the soft tissues The tremendous effect of such a slight and apparently insignificant lesion is well exemplified by the occasional occurrence of paralytic ileus following fracture of the ribs (Christopher<sup>22</sup>) There have been many observations, both clinical and experimental, that sclerosis of the arteries results when nerves are injured or stimulated (Stapford,<sup>23</sup> Todd,<sup>24</sup> Schaeffer,<sup>25</sup> Shaw) To the case under consideration Manouelian's<sup>26</sup> findings are particularly applicable He incised the pericardium of an animal and removed a nerve filament going to the pulmonary artery At autopsy, sixty-five days later, a sclerosed plaque was found in the part of the vessel that was deprived of its nerve supply

Lesions of the systemic circulation similar to this one have been described by Evans,<sup>27</sup> Fishberg<sup>28</sup> and Kernohan, Anderson and Keith<sup>29</sup> They occur in the kidney, less frequently in other organs, and consist of a diffuse hyperplastic sclerosis, mainly of the arterioles, associated with hypertrophy of the left side of the heart and a high blood pressure The etiology is unknown, although it has been considered to be involutionary Jores<sup>30</sup> thought it the result of stress We regard the present case as a pure example of this disease entity with the manifestation of the pathology and pathologic physiology limited to the lungs, the lesser circulation and the right side of the heart, and suggest that it be classified as sclerosis of the arteries

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18 Shaw, R Cunliff *Quart J Med* **19** 203, 1926

19 Pearce, R M *Bull Johns Hopkins Hosp* **17** 94, 1906

20 Palentini, D B *Arch per le sc med* **43** 63, 1920

21 Moschowitz, Eli *Am J M Sc* **174** 388, 1927

22 Christopher, F *Ann Surg* **90** 394, 1929

23 Stapford, J S B *Lancet* **1** 465, 1918

24 Todd, T W *J Nerv & Ment Dis* **40** 439, 1913, *Anat Rec* **8** 243, 1914, *J Anat & Physiol* **47** 250, 1913

25 Schaeffer, J P *Pennsylvania M J* **34** 786, 1931

26 Manouelian, Y *Ann Inst Pasteur* **27** 14, 1913

27 Evans, G *Quart J Med* **14** 215, 1920

28 Fishberg, A M *Anatomic Findings in Essential Hypertension*, *Arch Int Med* **35** 650 (May) 1925

29 Kernohan, J W, Anderson, E W, and Keith, N M *The Arterioles in Cases of Hypertension*, *Arch Int Med* **44** 395 (Sept) 1929

30 Jores, L *Wesen und Entwicklung der Arteriosklerose*, Munich, J F Bergmann, 1903

There has been a gradual change in the knowledge concerning sclerosis of the pulmonary artery. According to the researches of Yater and Konstam,<sup>31</sup> it was first described by Vieussens in 1706. Subsequent discussion appeared in 1816 (Kieysig), 1826 (Louis), 1828 (Laennec), 1829 (Andral) and 1835 (Boulland). The modern conception began with the papers of Posselt,<sup>32</sup> Saunders,<sup>33</sup> Giroux,<sup>34</sup> Veale and Coombs,<sup>35</sup> Eppinger and Wagner,<sup>36</sup> Mattiolo,<sup>37</sup> and Gamna,<sup>38</sup> although Romberg<sup>39</sup> (1891) and Aust<sup>40</sup> (1892) roughly constructed the picture. In 1901 Abel Ayerza, in a clinical lecture, described the syndrome of hypertrophy of the right ventricle associated with polycythemia, cyanosis and dyspnea. He gave it the name of "cardiacos negros." The term "Ayerza's disease" was introduced years later and used to designate sclerosis of the pulmonary artery, either primary or secondary (Waithin<sup>3</sup>). Later it was used for those cases due to syphilis (Cheney<sup>9</sup>). In view of the attendant confused nomenclature we suggest that "Ayerza's syndrome" should be limited to designating the complex of symptoms associated with "black cardiacs." It should not be used in the sense of designating any specific pathologic process, whether syphilitic or otherwise.

The association of paroxysmal dyspnea (asthma) with this case is interesting. It did not appear until after the symptoms had been present for six years, and it disappeared six months before death. Its failure, except on occasion, to respond to ephedrine and epinephrine therapy and the negative results from desensitization definitely place this case outside the general run of cases. Morbid changes in the bronchi were similar to those described for mild cases of asthma (Monckeberg,<sup>41</sup> Huber and Koessler<sup>42</sup>). The same changes could be explained on different grounds. Falta<sup>43</sup> and Eppinger and Hess<sup>44</sup> showed that pul-

31 Yater, W. M., and Konstam, G. R. *M. Clin. North America* **12** 1689, 1929.

32 Posselt, A. *Ergebn. d. allg. Path. u. path. Anat.* **13** 398, 1909, *Wien Arch. f. inn. Med.* **11** 357, 1925.

33 Saunders, W. E. Primary Pulmonary Arteriosclerosis with Hypertrophy of the Right Ventricle, *Arch. Int. Med.* **3** 257 (April) 1909.

34 Giroux, Leon. *Arch. d. mal. du cœur* **3** 595, 1910.

35 Veale, P. J., and Coombs, C. *Brit. J. Child. Dis.* **12** 72, 1915.

36 Eppinger, H., and Wagner, R. *Arch. f. inn. Med.* **1** 83, 1920.

37 Mattiolo, G. *Arch. per le sc. med.* **44** 124, 1921.

38 Gamna, C. *Pathologica* **13** 207, 1921.

39 Romberg. *Deutsches Arch. f. klin. Med.* **48** 197, 1891.

40 Aust, C. *München med. Wchnschr.* **39** 689, 1892.

41 Monckeberg, J. G. *Verhandl. d. deutsch. path. Gesellsch.* **14** 173, 1909.

42 Huber, H. L., and Koessler, K. K. The Pathology of Bronchial Asthma, *Arch. Int. Med.* **30** 689 (Dec.) 1922.

43 Bertelli, Falta and Schwerger. *Ztschr. f. klin. Med.* **71** 23, 1910.

44 Eppinger, H., and Hess, L. *Vagotomie*, Berlin, A. Hirschwald, 1910, p. 60.

monary eosinophilia resulted from vagotonia, Pescatori,<sup>45</sup> that it accompanied any asphyxial phenomenon Winternitz and co-workers<sup>46</sup> stimulated bronchial epithelial proliferation in animals by the insufflation of acids, and Eppinger and Wagner<sup>36</sup> have demonstrated the rôle of the lung in lactic acid metabolism Hypertrophy of the bronchi commonly results from overwork Chronic bronchitis is constantly associated with impaired pulmonary circulation and the liberation of blood pigments (Boyd<sup>47</sup>) It must be considered that the mild and atypical clinical and pathologic evidences of asthma were either concomitant with the pulmonary arteriosclerosis or associated with it in some way other than as an etiologic factor

Careful examination into the family did not reveal a hereditary factor (Kidd,<sup>48</sup> Clark and co-workers<sup>49</sup>) No infarcts formed (Loubry and Thomas,<sup>50</sup> and McCann and Stephens<sup>15</sup>) despite the grave vascular damage We agree with Clark that the diffuse diopsy is more an evidence of a toxic or privational metabolic disturbance than of a simple mechanical breakdown While the erythrocytes as counted numbered only 5,200,000, undoubtedly their number would have been found to be higher (Weber and Bode<sup>10</sup>) if failure of cooperation had not prevented their being counted later in the disease

#### CONCLUSIONS

A case of hyperplastic sclerosis of the pulmonary artery and arterioles is reported The distinguishing features, clinical and pathologic, between this disease and syphilitic sclerosis of the pulmonary artery are discussed The associated factors of etiologic importance were a prior attack of influenzal pneumonia, increased epinephrine in the circulating blood, stimulation, probably reflexly, of the nerves supplying the pulmonary artery, and asthma

The term "Ayerza's disease" should not be used synonymously with sclerosis of the pulmonary artery, since the pathologic process may be present for years before the complex of symptoms which Ayerza described make their appearance

45 Pescatori, F Riv di path e clin d tuberc **4** 735, 1930

46 Winternitz, M C , Smith, G H , and McNamara, F P J Exper Med **32** 205, 1920

47 Boyd, William Pathology of Internal Diseases, Philadelphia, Lea & Febiger, 1931, p 137

48 Kidd, P Tr Clin Soc, London **37** 192, 1904

49 Clark, R C , Coombs, C F , Hatfield, G , and Todd, A T Quart J Med **21** 51, 1928

50 Loubry, W , and Thomas, M Bull et mem Soc med d hôp de Paris **51** 9, 1927

# PEPTIC ULCERS (GASTRIC, PYLORIC AND DUODENAL)

OCCURRENCE IN GUINEA-PIGS FED ON A DIET DEFICIENT IN VITAMIN C

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AND

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RAY BROOK, N Y

The etiology of peptic ulcer in man is unknown. Heredity, occupation, infections, tobacco, alcohol, worry and trauma of the mucous membrane from hot foods have been suggested as etiologic factors, but are inadequate explanations. The relation of vitamins to tuberculous ulceration of the intestine as demonstrated in our previous studies<sup>1</sup> suggested that peptic ulcer might be due to a deficiency of certain vitamins in the dietary.

## HISTORIC REVIEW

The following data also suggest that peptic ulcer may be related to the dietary. The incidence of peptic ulcer varies in different countries: 0.8 per cent in Russia, 1.3 per cent in North America, 5 per cent in England and Germany and 16 per cent in Denmark. A marked increase in the incidence of peptic ulcer occurred in Russia and Germany during the period of partial starvation which followed the World War (from 1914 to 1918).<sup>2</sup> Hutter<sup>3</sup> stated that the peak of incidence of peptic ulcer occurs during the late winter and early spring. This type of ulcer is commonly associated with malnutrition in infants.<sup>4</sup>

Rosenow<sup>5</sup> found peptic ulcers in sheep, cows and calves at the Armour abattoir in Chicago. He was told that "the incidence of ulcer

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From the New York State Hospital for Incipient Pulmonary Tuberculosis

1 (a) McConkey, M. Treatment of Intestinal Tuberculosis with Cod Liver Oil and Tomato Juice, *Nat. Tuberc. A. Tr.* **25** 105 (May) 1929. (b) Smith, D. T., and McConkey, M. Experimental Intestinal Tuberculosis in the Guinea-Pig Induced by Feeding Tubercle Bacilli to Animals Living on a Diet Deficient in Vitamins, *ibid.* **25** 627 (May) 1929.

2 Cecil, Russell L. A Textbook of Medicine, Philadelphia, W. B. Saunders Company, 1930, p. 688.

3 Hutter, K. Seasonal Variations in Occurrence of Gastric and Duodenal Ulcers, *J. A. M. A.* **91** 2030 (Dec. 22) 1928.

4 Holt, Luther Emmett. Diseases of Infancy and Childhood, ed. 12, New York, D. Appleton and Company, 1923, p. 337.

5 Rosenow, Edward C. Etiology of Spontaneous Ulcer of Stomach in Domestic Animals, *J. Infect. Dis.* **32** 384 (May) 1923.

in the cow and the sheep was highest each year during the latter part of the winter and early spring months and that in their opinion the ulceration was the result of eating dry, coarse foods during these months, since the condition disappeared almost entirely each year during the summer and fall months when the animals were on pasture" Ivy<sup>6</sup> reported that peptic ulcer is rare in healthy dogs. In nine hundred autopsies he found only one ulcer (0.11 per cent). The animal was old and emaciated. On the other hand, as high as 2.5 per cent of peptic ulcers has been reported by Rosenow<sup>5</sup> among animals killed by gas in a dog-pound. Underhill and Mendel<sup>7</sup> found duodenal ulcers in dogs fed a diet of cooked meat, crackers, lard and beans.

Most of the experimental work on deficiency of vitamin C has been confined to guinea-pigs. In 1895, Theobald Smith<sup>8</sup> noted that in guinea-pigs fed a diet of bran and oats a peculiar disease characterized by subcutaneous and submucosal extravasation of blood developed, but in a recent personal communication he said that no true ulceration in the region of the duodenum was noted. Holst and Frolich,<sup>9</sup> in their studies on experimental scurvy (1907), noted the occurrence of peptic ulcer with occasional perforation in some of the guinea-pigs. The diet on which the animals were fed consisted of bread and grains of different types. McCarrison,<sup>10</sup> in 1919, fed nine guinea-pigs a diet of crushed oats and autoclaved milk, and in three he found necrotic ulcers in the stomach. "These changes," he said, "were present in the gastro-intestinal tract of guinea pigs dying in consequence of this dietary, although none of the animals presented the characteristic naked-eye appearances of scurvy. In a clinical sense, then, they may be regarded as prescorbutic." The same investigator also fed four guinea-pigs on a diet of autoclaved rice. At necropsy all the animals showed marked congestion of the duodenum, and one had a well marked ulcer extending to the peritoneal coat. In 1931, McCarrison<sup>11</sup> repeated his experiments on guinea-pigs and obtained data on the various stages of development in duodenal ulcers. He also reported the production of gastric ulcers in

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6 Ivy, A. C. Studies on Gastric Ulcer, *Arch. Int. Med.* **25**: 6 (Jan.) 1920.

7 Underhill, F. P., and Mendel, L. B. A Dietary Deficiency Canine Disease, *Am. J. Physiol.* **83**: 589, 1928.

8 Smith, Theobald. Investigation of Diseases of Domestic Animals, U. S. Dept. Agric., Bur. Animal Industry, Ann. Rep. 12 and 13, 1895, p. 171.

9 Holst, Axel, and Frolich, Theodor. Experimental Studies Relating to Ship-Beri-Beri and Scurvy, *J. Hyg.* **7**: 634, 1907.

10 McCarrison, Robert. Studies in Deficiency Disease, New York, Oxford University Press, 1921, p. 95.

11 McCarrison, Robert. Some Surgical Aspects of Faulty Nutrition, *Lancet* **1**: 1151 (May 23) 1931.

rats fed on a deficient diet Hess<sup>12</sup> mentioned the occurrence of duodenal ulcers in scorbutic guinea-pigs, but gave no data as to their frequency Magee, Anderson and McCallum<sup>13</sup> fed guinea-pigs on diets deficient in vitamin C and in minerals In one series, peptic ulcers, one of which perforated, developed in seven of thirty-two guinea pigs From each of fifteen additional guinea-pigs one suprarenal gland was removed, and the animals were then given the deficient diet Peptic ulcers developed in four of them

Peptic ulcer was not mentioned as a manifestation of scurvy by Jackson and Moore,<sup>14</sup> McCollum and Pitz,<sup>15</sup> Cohen and Mendel<sup>16</sup> and Sherman, LaMer and Campbell,<sup>17</sup> although they all noted the occurrence of intestinal hemorrhage These observers generally used young guinea-pigs and attempted to produce acute scurvy

#### EXPERIMENTS

We noted while studying the effect of deficiency of vitamins in relation to production of intestinal tuberculosis in the guinea-pig<sup>1b</sup> that peptic ulcer was associated with scorbutic lesions The following experiments were conducted to learn, if possible, the factor or factors responsible for the development of peptic ulcer in the guinea-pig

The guinea-pigs used in the following experiments were raised in our laboratory The stock diet consisted of hay, water, cabbage, carrots and a mixture of dry food containing 25 per cent white bread, 25 per cent bran, 24 per cent whole wheat flour, 15 per cent dry skimmed-milk powder, 5 per cent linseed oil meal, 5 per cent bone meal and 1 per cent sodium chloride In animals raised and maintained on this diet spontaneous peptic ulcer did not develop A routine examination of 1,000 guinea-pigs which either died spontaneously or were killed during various experiments failed to reveal an instance of peptic ulcer

EXPERIMENT 1—(Feb 17, 1928) Eleven adult guinea-pigs were given a diet of autoclaved milk, rolled oats and hay ad libitum This diet was almost completely deficient in vitamin C and relatively deficient in vitamins A and D After three weeks the animals lost weight, and a few showed swollen gums, suggesting

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12 Hess, A E Scurvy, Past and Present, Philadelphia, J B Lippincott Company, 1920

13 Magee, H E, Anderson, W, and McCallum, J Diet and Peptic Ulcer in Cavies, *Lancet* **1** 12 (Jan 5) 1929

14 Jackson, Leila, and Moore, J J Studies in Experimental Scurvy in Guinea Pigs, *J Infect Dis* **19** 478, 1916

15 McCollum, E V, and Pitz, W Vitamin Hypothesis and Deficiency, *J Biol Chem* **30** 229, 1917

16 Cohen, B, and Mendel, L B Experimental Scurvy of the Guinea Pig in Relation to the Diet, *J Biol Chem* **35** 425, 1918

17 Sherman, LaMer and Campbell Quantitative Determination of the Anti-scorbutic Vitamin C, *J Am Chem Soc* **44** 165 (Jan) 1922



scurvy Each animal was then given a single administration of 5 cc of canned tomato juice by pipet The scorbutic symptoms disappeared but recurred within a week This procedure was repeated a number of times in an effort to keep the animals in a prescorbutic state All died between the sixth and eighth weeks of the experiment At necropsy three of the guinea-pigs presented peptic ulcers In one there were multiple ulcers on the lesser curvature of the stomach near the pylorus, in another both duodenal and pyloric ulcers were present (fig 1), and in the third, a large perforated ulcer in the first portion of the duodenum, with a generalized peritonitis (fig 2) A fourth animal showed an erosion of the mucosa of the duodenum All animals presented varying degrees of scorbutic changes in the epiphyses, subcutaneous tissues, gums and suprarenals

EXPERIMENT 2—(Feb 17, 1928) Ten adult guinea-pigs were given the same diet as in experiment 1, and similarly maintained in a prescorbutic state by periodic

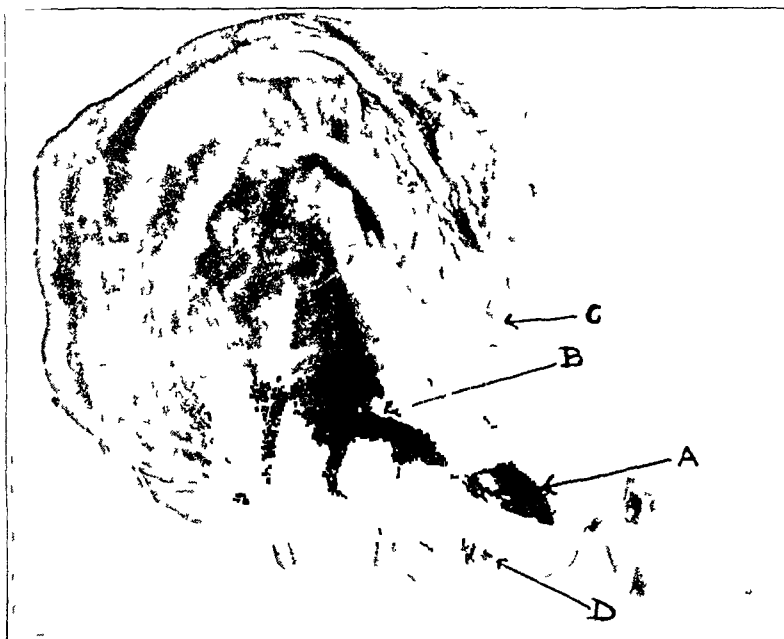


Fig 1—Perforated duodenal and pyloric ulcers A, duodenal ulcer, B, pyloric ulcer, C, lesser curvature of the stomach, and D, ampulla of Vater

administration of tomato juice In addition they received 1 mg of a culture of human tubercle bacilli in gelatin capsules by mouth twice each week All animals died between the sixth and eighth weeks At necropsy three animals presented peptic ulcers in the duodenum, one of these was an acute hemorrhagic lesion, whereas the others were deep and crater-like, with indurated walls One ulcer perforated, producing a generalized peritonitis All the animals presented scorbutic changes comparable to those noted in experiment 1 Two animals had small tuberculous ulcers in the cecum The ulcers in the duodenum, however, were not tuberculous, as was demonstrated by microscopic sections

EXPERIMENT 3—(Feb 17, 1928) Ten adult guinea-pigs were given the same basic diet used in experiments 1 and 2, but supplemented by 8 cc of tomato juice and 0.3 cc of cod liver oil daily The tomato juice was fed to each animal with a pipet, and the cod liver oil was given in capsules One milligram of a culture of human tubercle bacilli was given in capsules twice each week The animals remained in excellent condition for two months Two died between the second and

third months of generalized tuberculosis. The remaining eight animals had extensive tuberculous lesions of the liver, spleen and lungs when they were killed after three and one-half months. One of the animals had a peptic ulcer on the lesser curvature of the stomach. None of the remaining nine animals showed any evidence of scurvy or of peptic ulcer at necropsy.

*Comment on Experiments 1, 2 and 3*—In three of eleven adult guinea-pigs maintained on a diet partially deficient in vitamins A, C and D peptic ulcers developed. Most of the remaining eight animals showed congestion, hemorrhage or superficial erosions in the duodenum. Ten adult guinea-pigs were given the same diet and in addition fed tubercle bacilli. In three of the animals duodenal ulcers developed which were not tuberculous, as shown by microscopic sections. In experiment



Fig 2—Arrow points to perforated ulcer of the first portion of the duodenum

3, ten guinea-pigs were given the basic diet used in experiments 1 and 2, and tubercle bacilli by mouth, as in experiment 2, but the diet was supplemented by 0.3 cc of cod liver oil and 8 cc of tomato juice daily. Although in these animals extensive generalized tuberculosis developed, only one showed peptic ulcer. This indicates that the ulcers found in experiment 2 were due to the deficient diet and not to the action of the tubercle bacilli.

In experiments 1 and 2, as in those of Holst and Fiolich<sup>9</sup> and McCarrison,<sup>18</sup> the diets were probably deficient in vitamins A and D, as well as in vitamin C. The diets of Magee and Anderson and McCallum<sup>13</sup> were deficient in minerals as well as in vitamin C. In the following studies we attempted to determine what deficiency of vitamin or vitamins is responsible for peptic ulcer.

<sup>18</sup> McCarrison (footnotes 10 and 11)

EXPERIMENT 4—(April 4, 1929) We employed the scorbutic diet of Sherman, LaMer and Campbell,<sup>17</sup> which is deficient in vitamin C alone. Ten guinea-pigs were given this diet, which consists of whole ground oats, 59 per cent, skimmed milk powder (treated with heat to destroy the vitamin C), 30 per cent, butter fat, 10 per cent, and salt, 1 per cent. This diet is completely deficient in vitamin C. The animals lost weight rapidly after the second week. They were killed between the sixteenth and the twenty-second days of the experiment. Two showed acute ulceration limited to the mucosa of the duodenum. Seven presented hemorrhage into the ampulla of Vater. Only one guinea-pig had a normal intestinal tract. All ten animals presented the characteristic signs of scurvy in epiphyses, subcutaneous tissue, gums and suprarenal glands.

Ten control guinea-pigs were given the same diet supplemented by 8 cc of tomato juice. All of them remained in good health and at necropsy six weeks later presented no abnormalities.

EXPERIMENT 5—(Aug 1, 1929) As vitamin B is known to be related to certain intestinal disturbances, we performed the following experiment to determine whether a lack of this vitamin in the diet would produce intestinal ulcers.

Five guinea-pigs weighing from 250 to 300 Gm were fed on water and the following mixture ad libitum: polished rice, 79 per cent, casein, 20 per cent, and salt, 1 per cent. This was supplemented by 0.3 cc of cod liver oil daily to supply vitamins A and D and 10 Gm of banana daily to supply vitamin C. The oil and the banana were fed to each animal individually. The banana is fairly rich in vitamin C and very poor in vitamin B. No hay was allowed, the animals being bedded on sawdust. After two weeks on this diet the guinea-pigs lost their appetites. At this time small amounts of brewer's yeast were given at irregular intervals in an effort to restore their appetites. All five animals died between the fourth and sixth weeks of the experiment. Peripheral neuritis developed in two of them. Two had severe diarrhea, and one died with a volvulus of the ileum. General atrophy of the intestinal mucosa was found but no evidence of scurvy in the gums, epiphyses, subcutaneous tissue or suprarenal glands, and no hemorrhage or ulceration in the stomach or duodenum.

*Comment on Experiments 4 and 5*—Experiment 4 indicates that peptic ulcer in the guinea-pig is a result of deficiency in vitamin C alone. The addition of vitamins A and D to the diet failed to prevent the appearance of the ulcers, while the presence of vitamin C completely prevented their development. In experiment 5 the diet deficient in vitamin B produced lesions characteristic of deficiency in vitamin B, but there were no hemorrhages in the intestinal mucosa and no evidence of peptic ulceration.

It is conceded that under ordinary conditions man practically never lives on a diet as completely deficient in vitamin C as that used in experiment 4. We thought it advisable to see how closely we could imitate the diet eaten by the ordinary human being and still obtain the development of chronic peptic ulcers in guinea-pigs. We found that we could give most of the staple articles of the human diet, provided fresh fruits and fresh vegetables were omitted. A mixture was made which contained 20 per cent of baker's white bread (dried and ground), 20 per cent of chipped beef (ground and dried), 20 per cent of potato chips

(ground), 15 per cent of uncooked rolled oats, 15 per cent of skimmed milk powder and 10 per cent of sugar. Salt was present in the potato chips and chipped beef. This mixture is quite palatable even to the human taste, and the guinea-pigs ate it with relish. The skimmed milk powder was not heated to destroy its content of vitamin C, so the diet was only partly deficient in this vitamin. For the sake of convenience, we shall refer to this as human diet 2. That this diet is not inherently injurious to guinea-pigs is shown by an experiment in which we raised young guinea-pigs to maturity on it by adding cod liver oil, 0.3 cc, and tomato juice, 8 cc, daily. The guinea-pigs failed to deliver living young. When a few cabbage leaves were supplied, however, breeding took place in a normal manner.

EXPERIMENT 6—(March 3, 1929) Ten adult guinea-pigs were given human diet 2, hay and water ad libitum. They ate with avidity and grew very fat. Between the third and fourth weeks of the experiment the appetite began to fail, and the animals died between the eighth and twelfth weeks. Two of the ten animals had duodenal ulcers, one of which perforated. At necropsy there was very little evidence of scurvy, but most of the animals showed either congestion, hemorrhage or superficial erosion of the duodenum.

EXPERIMENT 7—(May 25, 1929) Eight adult guinea-pigs were given human diet 2 with hay and water ad libitum, supplemented by 0.3 cc of cod liver oil daily. The cod liver oil was fed individually to the guinea-pigs from a syringe. Two died of perforated duodenal ulcers, one at the end of the second month and another at the end of the fourth month. The latter ulcer had the macroscopic and microscopic characteristics of a chronic peptic ulcer. All animals were well nourished and presented only slight evidence of scurvy other than congestion and hemorrhage into the duodenum.

EXPERIMENT 8—(May 25, 1929) Ten adult guinea-pigs were given human diet 2, hay and water ad libitum. In five animals this diet was supplemented by 10 cc of tomato juice, and in the other five, by 10 cc of tomato juice and 0.3 cc of cod liver oil. All the animals remained in excellent nutrition until they were killed four months later, when no evidence was found of scurvy or of ulceration in the intestinal tract.

*Comment on Experiments 6, 7 and 8*—With this diet of bread, meat, milk, potatoes, rolled oats and sugar, peptic ulcers developed in four of eighteen guinea-pigs. The addition of cod liver oil to the diet did not prevent the development of the ulcers, whereas the daily addition of 10 cc of tomato juice completely protected the animals from the lesions.

In experiments 9 and 10 the relation of diet to intestinal tuberculosis and peptic ulcer was again investigated.

EXPERIMENT 9—(April 15, 1929) Twenty-one adult guinea-pigs were given water, hay and human diet 2 ad libitum. In addition, 0.5 cc of sputum which contained tubercle bacilli was given daily with a 1 cc tuberculin syringe. The animals received periodically small doses of tomato juice, as in experiments 1 and 2. They died from one to three months later, and several had tuberculous

ulcers of the ileum In addition, three duodenal ulcers and one jejunal ulcer were found, the latter having perforated Microscopic study revealed no evidence of tuberculosis in the peptic ulcers Most of the animals showed mild lesions of scurvy, but some did not Several of the animals showed congestion, hemorrhage and erosion of the duodenum

EXPERIMENT 10—(April 15, 1929) Thirty-six adult guinea-pigs were given water, hay and human diet 2 ad libitum They all received daily 0.5 cc of sputum which contained tubercle bacilli In ten animals the diet was supplemented by 10 cc of canned tomato juice daily, in sixteen, by 0.3 cc of cod liver oil and 10 cc of canned tomato juice, and ten received daily two or three cabbage leaves each, as a supplementary feeding A few animals died between the second and third months of the experiment with generalized tuberculosis The others were killed at the end of the fourth month, when the experiment terminated None of the thirty-six animals presented any evidence at necropsy of hemorrhage or ulceration of the intestinal tract

*Comment on Experiments 9 and 10*—Of the twenty-one guinea-pigs maintained on human diet 2 and fed with sputum containing tubercle bacilli, duodenal ulcers developed in three, and a jejunal ulcer in one That tubercle bacilli were not a factor in causing these ulcers is shown by experiment 10, in which thirty-six guinea-pigs were fed tuberculous sputum and maintained on the same diet supplemented by either tomato juice, cod liver oil and tomato juice, or cabbage leaves None of the thirty-six animals fed on this supplemented diet presented lesions in the stomach or duodenum, although they all had extensive generalized tuberculosis

The initial break in the mucosa in peptic ulcer may be caused by a variety of agents mechanical, chemical, nervous, bacterial or dietary But if our theory is correct, an abundance of vitamin C is essential for healing, regardless of the primary cause In the following experiment mechanical injury was done to the mucosa of the stomach and duodenum Some animals were maintained on an adequate diet throughout the experiment, and others were given an adequate diet only after operation, while still others were on an inadequate diet throughout Comparative studies were made on the healing of ulcers in the animals of different groups

EXPERIMENT 11—(April 15, 1929) Fifteen normal adult guinea-pigs were selected Five of them were fed on our ordinary stock diet throughout the experiment and served as control animals The other ten animals received a diet of rolled oats, autoclaved milk and hay ad libitum, supplemented by 0.3 cc of cod liver oil fed individually each day After fifteen days of this diet none of the animals showed gross evidence of scurvy, although we knew from previous experiments that scurvy would have appeared in an additional week or ten days

All animals were subjected to the following procedure They fasted for twenty-four hours previous to the operation Each one was given 5 cc of a 50 per cent solution of dextrose immediately before the operation Under ether anesthesia the peritoneum was opened, and a purse-string suture with silk was made in the ante-

rior wall of the stomach. Through the center of this an opening was made with a cautery. A dental burr was then introduced as far as the duodenum, and the mucosa of the duodenum was scarified. The dental burr was withdrawn, and the opening in the stomach was closed with the purse suture. The peritoneum, the muscle, the subcutaneous tissue and the skin were in turn sutured with black silk. Each of the animals was given 5 cc of a 50 per cent solution of dextrose immediately after the operation. One of the fifteen guinea-pigs died at the induction of the anesthesia. This animal, which had been fed the deficient diet for fifteen days, was found to have an erosion in the mucosa of the duodenum, although there was

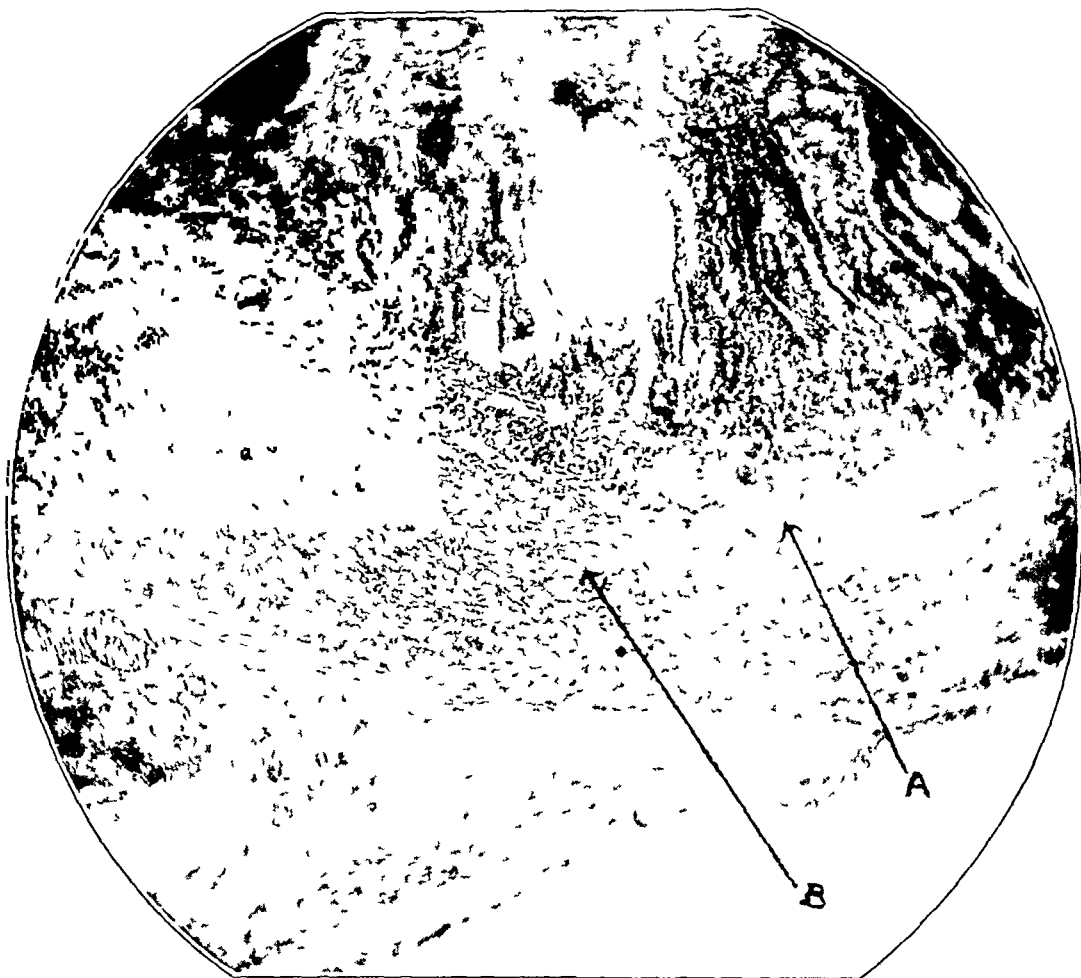


Fig 3—Hemorrhage into the wall of the duodenum with necrosis and sloughing of part of the mucosa. A, hemorrhage into the submucosa, B, hemorrhage into the muscularis.

no gross evidence of scurvy in other parts of the body. The remaining animals survived, in none of them did peritonitis develop.

Five guinea-pigs were maintained on the stock diet throughout the experiment. Five of the ten animals which were fed on the diet deficient in vitamin C before operation remained on that diet. The other four animals on this diet previous to operation were subsequently given 10 cc each of canned tomato juice daily. Although there was no evidence of scurvy in these nine guinea-pigs at the time of operation, it was noted that they bled more readily, and that the edges of the cut tissues became more hemorrhagic and edematous following operation than did the wounds in the animals on an adequate diet.

The incision in the skin of the five animals fed on the stock diet was completely healed in ten days, and when the animals were killed three weeks later, the mucosa of the duodenum was so well restored that it was impossible to see any evidence of previous injury. The cautery wound into the wall of the stomach was entirely healed, and was located only by the presence of the black silk suture.

In the four animals which were fed a diet deficient in vitamin C before the operation and which were given tomato juice afterward the incision in the skin also healed completely after eighteen days. When the animals were killed three weeks after the operation, the mucosa of the stomach and the duodenum was likewise restored to normal. There was still, however, some edema of the subcutaneous tissue.

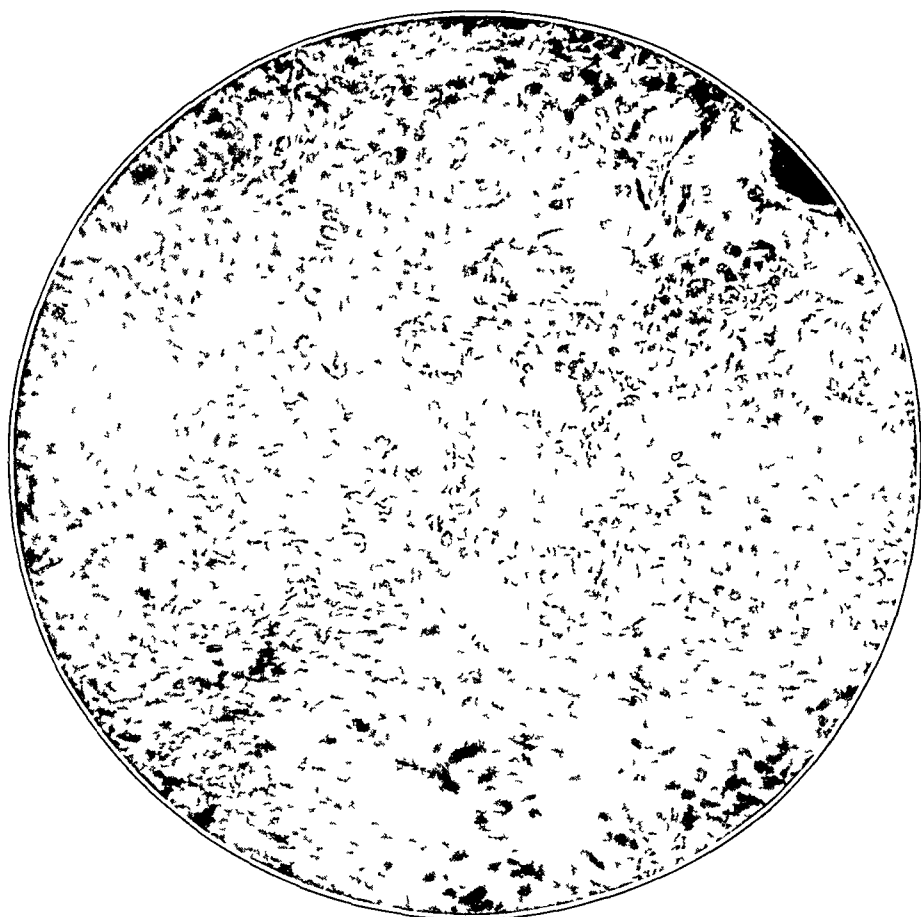


Fig 4—A higher magnification of the hemorrhagic areas in the submucosa and muscularis seen in figure 3. The area in the center of the photograph consists mainly of disintegrated red cells. There is an occasional intact red blood cell.

The five guinea-pigs which remained on the diet deficient in vitamin C throughout the experiment died from one to two weeks after the operation. The incision in the skin showed no evidence of healing, the cautery wound of the stomach showed ulcers in two animals, and four of the five showed large ulcers in the duodenum.

*Comment on Experiment 11*—Fourteen adult guinea-pigs were subjected to operative trauma of the stomach and duodenum. Five animals used as controls were maintained on an adequate diet throughout the

experiment, and were killed three weeks after the operation. At necropsy no lesions were observed in the intestinal tract, and the wounds in the stomach and duodenum were found to be soundly healed.

The nine animals fed on a diet deficient in vitamin C were operated on on the fifteenth day of the experiment, while they were still in the prescorbutic stage. It was observed that they bled more freely, and that more edema of the injured tissues developed in them than in the controls.

Five were kept on the scorbutic diet after the operation. The operation consisted of mechanical removal of the mucosa from a portion of the duodenum. All the animals died between the seventh and fourteenth days following operation. Two presented ulcers at the site of the operative wound in the stomach, and four of the five animals showed large



Fig. 5—Low power magnification of a section taken from a duodenal ulcer which showed chronic changes in the floor.

duodenal ulcers. The four animals which were fed on a diet deficient in vitamin C before operation but which were given tomato juice subsequently recovered completely, no ulcers were present. The operative wound in the abdominal wall, however, was slower in healing in these animals than in those given an adequate diet throughout the experiment.

These experiments indicate that in the absence of an adequate supply of vitamin C, mechanical injury to the mucosa of the stomach and duodenum of the guinea-pig results in the development of ulcers. The same degree of mechanical injury in animals fed on a diet adequate in vitamin C results in rapid and complete healing.

#### PATHOLOGY

The usual site of the ulcers in the foregoing experiments was in the first portion of the duodenum just distal to the pyloric sphincter. A



few were present in the stomach in the pyloric portion near the lesser curvature. Single ulcers were the rule, and they were usually round or oval. Although a few ulcers presented irregular borders, most of them were punched-out in appearance. There was usually sufficient induration of the walls of the ulcer to be easily palpated from the outside of the viscus. Both perforation of the ulcers and fatal hemorrhage occurred several times. Lesser hemorrhages from the ulcer occurred more frequently, and extravasation of blood into the wall of the bowel was the most constant finding.

Figure 3 represents a section taken from a hemorrhagic area in the wall of the duodenum. Hemorrhage is present in the submucosa and

TABLE 1—*Results of Experiments with Chronic Deficiency in Vitamin C*

Experiment	Number of Animals	Number of Peptic Ulcers
1	11	3
2	10	3
4	10	2
6	10	2
7	8	2
9	21	4
11	5	4
	<hr/> 75	<hr/> 20

TABLE 2—*Results of Experiments with Adequate Vitamin C*

Experiment	Number of Animals	Number of Peptic Ulcers
3	10	1
4 (control)	10	0
5	5	0
8	10	0
10	36	0
11 (control)	9	0
	<hr/> 80	<hr/> 1

muscularis. The mucosa overlying the hemorrhage is necrotic, and part of it has sloughed out. A higher magnification of the submucosa and muscularis (fig. 4) shows a few intact red blood cells in the midst of many disintegrated cells.

Although most of the ulcers observed in our experiments were acute, some of them presented evidence of a chronic nature. Figure 5 is the study of a duodenal ulcer that occurred in an animal which had been fed the diet deficient in vitamin C for four months. A higher magnification of this lesion (fig. 6) shows round cell infiltration and a considerable number of fibroblasts in the floor of the ulcer.

Whether or not there is an initial thrombosis of the vessels in the area of the ulcer we are at present unable to say. In any case, hemorrhage into the wall of the duodenum in the region overlying the ulcer was an almost constant finding.

## TREATMENT OF PEPTIC ULCER IN MAN

The experiments recorded here indicate that peptic ulcer in the guinea-pig is due to a partial but chronic deficiency of vitamin C. This specific deficiency may or may not be the cause of peptic ulcer in man. If it is the cause, an abundance of vitamin C in the diet should aid in the healing of these lesions.



Fig 6—Higher magnification of the section in figure 5. Note the round cell infiltration and numerous fibroblasts in the floor of the ulcer.

Five patients with chronic duodenal ulcers have been treated at the sanatorium by supplementing the ordinary hospital diet with cod liver oil and tomato juice. This is the routine dietary for the treatment of intestinal tuberculosis at the New York State Hospital for Incipient Pulmonary Tuberculosis<sup>11</sup> and contains an abundance of other vitamins which may possibly be of value in the treatment of peptic ulcer. The number of patients treated is too small to warrant definite conclusions, but the small group responded favorably to the treatment for periods

lasting from six months to three years. Therefore it might be advisable to supplement the Sippy or Lenhartz diet with tomato or orange juice and cod liver oil.

#### CONCLUSIONS

1 Routine necropsies on 1,000 guinea-pigs maintained on our stock diet failed to show a single spontaneous peptic ulcer.

2 Of seventy-five guinea-pigs fed on diets deficient in vitamin C, in twenty, or approximately 26 per cent, peptic ulcers developed which were similar in location and in gross and microscopic appearances to those observed in man.

3 Of eighty guinea-pigs fed on corresponding basic diets supplemented by vitamin C, in only one did peptic ulcer develop.

4 Diets deficient in vitamins A, B and D did not cause peptic ulcers if the supply of vitamin C was adequate.

5 Mechanical injury to the mucosa of the duodenum in guinea-pigs fed on an adequate diet was followed by rapid and complete healing while similar injury to guinea-pigs fed on a diet deficient in vitamin C resulted in the formation of peptic ulcers.

6 Peptic ulcer in the guinea-pig is apparently caused by a partial but prolonged deficiency of vitamin C.

# INHERENT SENSITIVITY OF THE SKIN TO NICKEL AND COBALT

(ALLIED ELEMENTS IN GROUP VIII, PERIODIC SYSTEM)

SLOAN G STEWART, M D

PHILADELPHIA

Inherent sensitivity of the skin to nickel, in contrast to the acquired form, which has been found so frequently among those who work with nickel, seldom has been described. Allusions are made, however, to a "natural" susceptibility among certain workers, especially blond people and young women. Indeed, a real distinction may be made between inherent and acquired sensitivity of the skin to external sensitizing agents. In that group in which sensitiveness to nickel is acquired are placed those cases of "imitative dermatitis" in which, by repeated contact of the skin with solutions of nickel salts or finely divided particles of nickel dust, an eruption develops at the site of exposure. This does not imply a latent sensitivity, for after a certain period of exposure this lesion may develop under certain conditions of heat and moisture in any person exposed for a sufficiently long period. Quite analogous is the experiment described by Walthard,<sup>1</sup> in which he was able to produce a nickel dermatitis in guinea-pigs by repeatedly painting the skin with nickel sulphate.

The dermatitis of acquired sensitivity to nickel, usually occurring on the face, neck and other exposed parts, constitutes an important problem in industrial hygiene. The first comprehensive review of metal dermatitis, alluding to nickel dermatitis in workers exposed to nickel baths in the plating process, is that of Blaschko,<sup>2</sup> in 1889. This has been followed by extensive industrial surveys concerning the cause and prevention of nickel dermatitis, the most comprehensive of which are treatises by White,<sup>3</sup> Blumer and Mackenzie,<sup>4</sup> and Gron.<sup>5</sup>

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From the Allergy Section of the Medical Clinic, Hospital of the University of Pennsylvania

1 Walthard, B. Die Erzeugung experimenteller Nickelidiosynkrasie bei Laboratoriumstieren, Schweiz med Wchnschr **56** 603, 1926

2 Blaschko, A. Die Berufsdermatosen der Arbeiter, Deutsche med Wchnschr **15** 925, 1889

3 White, R. P. The Dermatergoses or Occupational Affections of the Skin, ed 3, London, H. K. Lewis & Co., 1928

4 Blumer, F. M. R., and Mackenzie, E. A. Studies in the Control and Treatment of "Nickel Rash," J Indust Hyg **8** 517, 1926

5 Gron, K. Nickelplater's Rash, Urol & Cutan Rev **33** 606, 1929

In the group of cases designated as showing inherent sensitivity to nickel are included those in which there is found a generalized sensitivity of the skin of the body to nickel when there has been no exposure to the metal. Inherent sensitivity may be similar to the so-called "focal sensitivity" of the skin, caused by absorption of a substance through the skin at one point producing sensitization of other parts through the blood stream. The extreme rarity of the condition, however, makes this explanation seem unlikely, when one considers how often nickel-containing objects touch the skin. Examples of inherent sensitivity to nickel are not common in the medical literature, and the brevity of most of the reports and the types of cases presented do not give an adequate clinical picture. In two of three reports that will be noted, the cutaneous lesions might be thought to be an irritative dermatitis, were it not for suggestive but inadequate patch tests.

McAlester, J<sup>1</sup>, and McAlester, III,<sup>6</sup> reported three cases of nickel dermatitis, with lesions involving the nose and the eyelids, the inception was in nickel used in white gold frames of spectacles. Patch tests to nickel made with a nickel coin on the forearm were positive. Three similar cases of dermatitis over the temples and ears were described by Lain.<sup>7</sup> This rash was relieved by the use of frames of glasses free from nickel. No cutaneous tests were made. In Rothman's<sup>8</sup> case is recounted the history of a counter of coins who worked for a tramway company and in whom "eczema" developed. Skin tests with nickel, silver and copper coins revealed a strongly positive reaction to nickel and a slightly positive reaction to silver and copper. Pure metals, however, were not used in the testing.

Inherent sensitivity of the skin to closely allied metals in the same (periodic) group, as observed for nickel and cobalt in the patient whose case is reported in this paper, must be most uncommon, for no description of this phenomenon has been found in the medical literature. This may be due to the fact that patch tests with pure metals have not attained the peak of prominence in dermatology and allergy that skin tests to pollens, foods and animal emanations have acquired, with the possible exception of the use of patch tests in determining sensitivity to arsphenamine.

#### REPORT OF A CASE

*History*—A G, a woman, aged 31, was seen as a private patient for desensitization to hay fever which occurred in the fall. The characteristic symptoms of hay fever had persisted for twelve years, starting about August 15, and lasting until the

6 McAlester, A W, Jr, and McAlester, A W, 3d. Nickel Sensitization from White Gold Spectacle Frames, *Am J Ophth* **14** 925, 1931.

7 Lain, E S. Nickel Dermatitis, *J A M A* **96** 771 (March 7) 1931.

8 Rothman, S. Hypersensitiveness to Metal Coins, *J A M A* **97** 336 (Aug 1) 1931.

first cold weather. Occasionally sneezing and epiphora were noted in the spring. Mild paroxysms of asthma occurred twice during the fall of 1931. Previous inoculations of pollen had been unsuccessful in effecting desensitization. Three years before, frequent outbreaks of "hives" had been the source of much discomfort, but had not been present during the past year. There had been no eczema. Two or three times a year, for several years, the patient had had attacks of nausea and vomiting, associated with mild left frontal headache. There was also a history of the development of itching papules and vesicles on the skin at various points of friction after exertion in hot weather. This was most marked in the antecubital spaces and the axillae.

The most unusual feature of this exceptionally allergic history related to an itching, burning rash described as "welts on the skin, which sometimes caused blisters and redness." The lesions always appeared at the sites of contact with certain metal objects in wearing apparel, such as a particular white gold wrist

TABLE 1—*Cutaneous Sensitization Tests (Scratch Tests)*

a Inhalants			
Chicken feather	0-5	Kapok	3-10
Goose feather	3-15	Cottonseed	5-20
Horse hair	4-12	Orris root	5-35
Sheep wool	2-5	Silk	4-8
Stock dust	6-25		
b Foods			
Egg	0	Orange	3-10
Wheat	0	Lettuce	5-20
Milk	0	Vanilla	3-15
Coffee	3-15	Tea	0
c Pollens			
<u>Ragweed, giant</u>	12-30	June grass	3-15
<u>Ragweed, short</u>	15-35	Orchard grass	4-15
Goldenrod	10-20	Timothy	5-15
Sweet vernal	3-10		

0 indicates a negative reaction, in readings recorded by two figures (3-15), the first figure (3) represents the diameter of the wheal in millimeters, and the second (-15), the diameter of the areola in millimeters.

watch, a gold bracelet, safety pins, suspensories and the like. The eruption would persist for from two to ten days. Yellow gold, silver and platinum induced no reaction.

The past medical history was unimportant except for the presence of a colloid goiter since puberty, which at times, especially during the past three years, increased somewhat in size.

The only family history of allergy was in the father, who for years had had hay fever. There was no history of urticaria, cutaneous disease or asthma.

*Physical Examination*—The patient was an active, healthy, cooperative person. The only positive findings on examination were hyperactive reflexes, a definite vasomotor instability and a diffuse, symmetrical enlargement of the thyroid gland. The blood pressure was 115 systolic and 80 diastolic, with an average pulse rate of 80.

*Laboratory Data*—The urine was normal. The red blood count averaged 4,600,000 cells, with a hemoglobin content of 82 per cent (Sahli). The leukocyte count was 9,000, with a normal differential count. At no time was eosinophilia found. The Wassermann reaction of the blood was negative. The basal metabolic

rate varied from —5 per cent to +1 per cent In table 1 are summarized the cutaneous tests to pollens, inhalants and foods

*Sensitization Tests of the Skin*—There was cutaneous sensitivity to all of the pollens tested, to many of the inhalants and to a few foods, but of these, symptoms were produced only by giant and short ragweed Desensitization with these pollens gave great relief from symptoms due to ragweed during each of the past two seasons

The clinical impression of multiple allergic reactions in the form of hay fever and asthma due to ragweed, urticaria, heat sensitivity and possibly migraine of mild type did not explain the peculiar cutaneous reaction experienced by contact with the accessory metallic articles used in feminine wearing apparel

*Patch Tests for Sensitivity to Metals*—In accordance with the technic instituted by Jadassohn<sup>9</sup> and reviewed by Schoch<sup>10</sup> in working with arsphenamine, patch tests of the skin were made, only pure elements of metals being used, especially those necessary for compounding in alloys It seemed likely from the history that the specific irritating substance would be found among the latter metals, because all of the offending articles were made of alloyed metals, whereas articles of yellow gold, silver and platinum produced no eruption A strong sensitiveness to nickel was discovered, as recorded in table 2

TABLE 2—*Cutaneous Sensitization Tests (Patch Tests)*

a Metals			
Zinc	0	Gold	0
Tin	0	Nickel	++++
Lead	0	Cobalt	+++
Aluminum	0	Iron (1)	+
Copper	0	Iron (2)	0
Silver	0		

The positive reaction obtained in specimen 1 of iron was a false positive reaction due to 1 per cent of contamination by nickel Specimen 2 of iron contained no nickel

The sensitivity of the skin to cobalt was determined only after the patient had brought a string of bluish-green beads that had caused an urticaria-like eruption encircling the neck The coloring pigment was the silicate of cobalt By patch test, as seen in the chart, cobalt gave almost as strong a cutaneous reaction as nickel Since cobalt and nickel are in the same periodic metal group with iron, in the ferrous series, patch tests were made with a small square of what was thought to be pure iron, but was subsequently found to contain traces of nickel, with a resultant slightly, but definitely, positive cutaneous reaction Other metals chosen from the first four groups of the periodic table gave negative patch tests Control patch tests made on fifteen normal and allergic persons were negative

*Type of Cutaneous Lesion*—The lesion represented in figure 1 was produced after twenty hours' contact with metallic nickel It was deep purple, slightly indurated with local edema, and covered with coalescing papular and vesicular efflorescences, which in small areas formed weeping surfaces This lesion produced intense itching and a sensation of burning Some of the smaller areas of dermatitis lasted only a few days, but the large areas produced by strongly positive tests

<sup>9</sup> Jadassohn, J Hautkrankheiten bei Stoffwechselanomalien, Fifth Internat Dermat Cong 1904, vol 2, p 231

<sup>10</sup> Schoch, A G Arsphenamine Sensitization Tests Including a Report of Arsenical Dermatitis Due to Arsenobenzol Radical of Bismarsen, Am J Syph 14 75, 1930

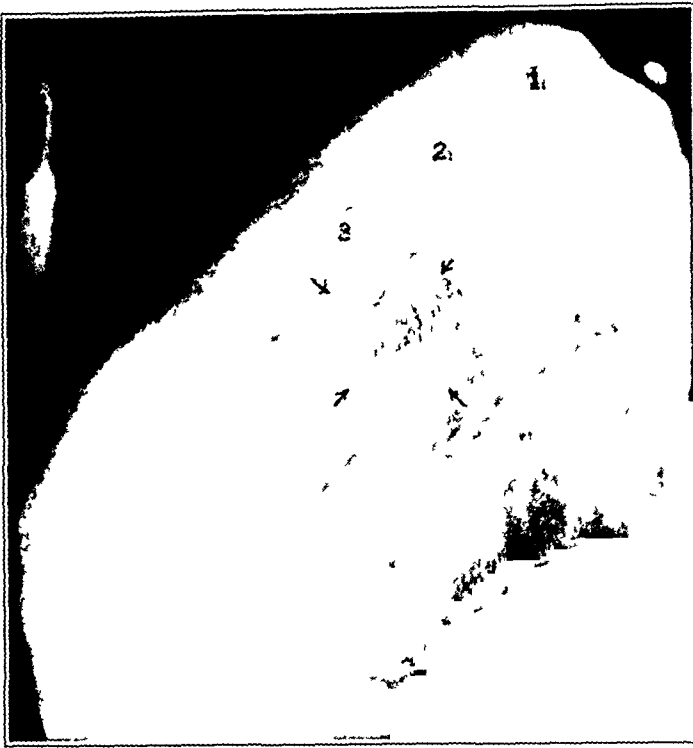


Fig 1—Photograph of patch tests with (1) aluminum, (2) copper and (3) nickel applied to the inner thigh. Note the swelling and the small vesicles where the nickel was in contact with the skin. Tests 1 and 2 were negative.



Fig 2—This sketch represents graphically the hyperemic, edematous, vesicular lesions produced by contact of nickel, *Ni*, cobalt, *Co*, iron, *Fe*, and a control metal, *C*, of equal size, with the skin of the patient.



persisted for as long as two or three weeks. This type of lesion has been classified as dermatitis venenata—a nonspecific term including such reactions as those produced by *Rhus toxicodendron*, *Primula obconica*, other plants and shrubs, arsphenamine and drug and chemical irritants.

*Patch Tests and Passive Transfer*—The patch tests were strongly positive to nickel and cobalt on any surface of the patient's skin, and, since there had never been any more exposure to nickel than occurs in the average nonsensitive person, it did not seem possible that the condition could be an acquired sensitiveness. No one in the patient's family had been in contact with nickel or cobalt, and patch tests with the same group of metals as were used on the patient were negative when applied to the father's and mother's skin. Passive transfer tests were done on a normal, nonallergic person according to the Prausnitz-Kustner method. Patch tests with nickel, cobalt and iron on the passive transfer areas were negative, and with ragweed pollen by scratch test, strongly positive. Patch tests with all of the metals on normal areas of skin were negative. There is no evidence that a specific substance circulates in the blood to cause this altered capacity for specific reaction in the skin to metallic antigens. This is in agreement with the negative results obtained by Lewith<sup>11</sup> and by Walthard<sup>1</sup> with nickel salts, and by Kesten and Laszlo<sup>12</sup> with other antigens causing dermatitis venenata.

*Nature of the Cutaneous Reaction*—The dermatitis resulting from contact with nickel was identical with that produced by cobalt. The speed of reaction when the pure metals were used varied from eight to sixteen hours, being influenced greatly by temperature and humidity, and secondarily, as will be pointed out in relation to the salts, by the solubility and rate of dissociation of those salts which form with perspiration. On cold days only a slight reaction could be induced in twenty-four hours by patch test. On hot days, and especially when the humidity was high, not only did the lesions appear more quickly, but they were much more intense. Reduction of the skin's resistance and increased irritability result from excessive alkaline sweat under such conditions (Pemberton<sup>13</sup>) and probably explain, in part, the variability of this reaction.

Lewith<sup>11</sup> in his investigations on those who worked with nickel made intradermal tests with various nickel salts and obtained positive reactions only with nickel sulphate. Control tests with 1 per cent sulphuric acid and with zinc and copper sulphate gave negative results. Schittenhelm and Stockinger,<sup>14</sup> using intracutaneous injections and compresses of nickel sulphate and chloride, obtained strongly positive reactions on previously attacked parts of the skin ("focal reaction").

In table 2 are summarized the results obtained from patch tests in which the crystals of various salts of nickel, cobalt and iron were used, applied to the skin of the patient, A. G., in dry form and sealed under gauze with squares of adhesive tape.

11 Lewith. Verhandl Dermat Gesellsch d Tschechoslowakô Republic, Feb 18, 1927, quoted by Gron.<sup>5</sup>

12 Kesten, B., and Laszlo, E. Dermatitis Due to Sensitization to Contact Substances, Dermatitis Venenata, Occupational Dermatitis, Arch Dermat & Syph **23** 221 (Feb) 1931.

13 Pemberton, R. A Summary of the Effects of External Heat Upon the Human Body, Am J M Sc **169** 485, 1925.

14 Schittenhelm, A., and Stockinger, W. Ueber die Idiosynkrasie gegen Nickel und ihre Beziehung zur Anaphylaxie, Ztschr f d ges exper Med **45** 58, 1925.

*Tests with Metal Salts*—The reactions listed in table 3 show definitely positive reactions to nickel and cobalt salts, as indicated by the plus marks. No rash was noted after application of either the unstable divalent or more stable trivalent salts of iron. This suggested the possibility of a false positive reaction to metallic iron. A chemical analysis of the metallic iron used for testing the skin revealed a contamination by nickel of less than 1 per cent. The patch test with iron was repeated, pure iron wire of high grade being used. After a negative cutaneous test with this was obtained, it was concluded that there was no skin sensitivity to iron. This experiment does serve, however, to illustrate the extreme delicacy of the reaction.

There was a variability in the intensity of the reactions, although the tests were performed under the same conditions of temperature and moisture. Another factor relating to the variability of these reactions must be the solubility and ionization of the salts of nickel and cobalt. The most violent reactions were produced by the nitrates. The solubility of the nitrates, sulphates and chlorides is recorded in table 3. The chlorides and acetates are also more soluble than the sulphates. A similar ratio applies at body temperature.

TABLE 3—*Cutaneous Reactions to Salts of Nickel, Cobalt and Iron (Patch Tests)*

No	Salts of Metals	Solubility at 30 C		Itching	Hyperemia	Edema	Vesicles
		Gm Ni or Co 100 Gm H <sub>2</sub> O					
1	NiCl <sub>2</sub>	29		+++	++	+	++
2	Ni(NO <sub>3</sub> ) <sub>2</sub>	35		+++	++	+++	+++
3	Ni(C <sub>2</sub> O <sub>2</sub> H <sub>3</sub> ) <sub>2</sub>			+++	+++	++	+
4	NiSO <sub>4</sub>	16		++	0	0	+
5	CoCl <sub>2</sub>	26		+++	++	+++	+++
6	Co(NO <sub>3</sub> ) <sub>2</sub>	36		++	+++	+	+
7	Co(C <sub>2</sub> O <sub>2</sub> H <sub>3</sub> ) <sub>2</sub>			+	+	+++	0
8	CoSO <sub>4</sub>	16		++	+	0	+
9	FeSO <sub>4</sub>			0	0	0	0
10	FeSO <sub>4</sub> (NH <sub>4</sub> ) <sub>2</sub> SO <sub>4</sub>			0	0	0	0
11	FeCl <sub>3</sub>			0	0	0	0
12	(Fe) <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub>			0	0	0	0

## SUMMARY AND CONCLUSIONS

The patient whose case is presented exhibited an inherent skin sensitivity to nickel and cobalt. In summarizing the data obtained from metal patch tests, certain facts stand out definitely. There is a group-specific reaction of the skin to nickel and cobalt. This reaction takes the form of dermatitis venenata, a type of lesion which is not specific. The most important factors influencing the speed and extent of the reaction are heat, moisture and the solubility of the salts used. Lastly, the chemical nature of the reaction is further suggested in the patch tests by the decreased time it required to obtain a reaction to the metallic salts in comparison with the time required for a reaction to pure metals.

That the reaction is not irritative is proved by negative control tests. That it is not an acquired sensitivity is supported by a negative history of exposure to or ingestion of the specific metals. Passive transfer tests suggest that there is no specific reacting substance in the blood, and that the reaction is a direct cellular one.

It would seem likely, therefore, that there exists a reaction, chemical in nature, between some specific complex molecule in the epidermal cells and the salts of nickel and cobalt. It is questionable that this should be interpreted as a truly allergic phenomenon, but such a conclusion is strongly suggested because of the similarity of the condition to allergic types of dermatitis venenata and because of its association with a multiplicity of coexisting allergic manifestations exhibited by the patient, i. e., hay fever, asthma, urticaria and migraine.

# DIRECT COMPARISON BETWEEN SPECIFIC AND NONSPECIFIC SERUM THERAPY FOR TYPE I LOBAR PNEUMONIA

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It has been suggested that the effects of specific serum therapy in type I lobar pneumonia are due, not to the specific antibodies contained in the serum, but to the nonspecific action of the intravenously administered horse serum proteins. Miller<sup>1</sup> and von den Velden,<sup>2</sup> as well as Hallermann and Kahler,<sup>3</sup> have made this suggestion because of the symptomatic changes they noted in lobar pneumonia following the injection of protein materials other than immune horse serum, such as typhoid vaccine, normal horse serum and normal human serum. Sonnenfeld<sup>4</sup> and Lichtenstein<sup>5</sup> have supported this suggestion because they occasionally observed striking clinical improvement in patients with pneumonia due to pneumococci other than type I following the administration of serum that presumably contained only type I pneumococcic antibodies.

An examination of the question from the point of view of those who have had extended experience with the specific serum, however, brings out the fact that the symptomatic and curative effects of the serum are probably due to its content of type-specific pneumococcic

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1 Miller, J. L. The Present Status of Nonspecific Therapy, *J. A. M. A.* **95** 464 (Aug. 16) 1930.

2 von den Velden, R. Klinisch-experimentelle Beiträge zur Kenntnis temperatur-herabsetzender Substanzen, *Deutsches Arch. f. klin. Med.* **113** 324, 1913-1914.

3 Hallermann, A., and Kahler, H. Ueber die Typeneinteilung der Pneumonie und ihre Behandlung mit Serum, *Klin. Wchnschr.* **9** 650, 1930.

4 Sonnenfeld, A. Serumtherapie der krupösen Pneumonie, *Deutsche med. Wchnschr.* **56** 569, 1930.

5 Lichtenstein, Hermann. Die Serumbehandlung der croupösen Pneumonie, *Med. Klin.* **25** 1966, 1929.

antibodies In experimental animals the beneficial action of the anti-pneumococcic serum has repeatedly been shown to depend on its type-specific character,<sup>6</sup> and extensive, carefully compiled clinical data of its use in man point to the same conclusion.<sup>7</sup> But even though the therapeutic effect of antipneumococcic serum depends on its content of specific antibodies, it is probable that some nonspecific action is also present. The following observations were made in order to attack the question of the extent and nature of the nonspecific effects.

A comparison was made between the effects of concentrated type I antipneumococcic serum and the effects of similarly concentrated normal and antimeningococcic horse serums containing no specific pneumococcic antibodies. The regularity of the symptomatic changes following the administration of type I antipneumococcic serum<sup>8</sup> made it seem likely that such a comparison would be clean-cut. The patients were observed with two questions in mind. The first concerned the relative therapeutic effectiveness of the specific and nonspecific horse serum globulins, and the second concerned the observation and description of the nonspecific effects in relation to the general subject of nonspecific therapy.

#### SUBJECTS, MATERIALS AND METHODS

Hospital cases of lobar pneumonia were studied in which the presence of type I pneumococci was determined before the end of the fourth day of the disease. The choice of specific or nonspecific therapy depended on the hospital service to which the patient was admitted, which was, in turn, entirely subject to chance. The general treatment employed in the various hospital services did not differ to any significant degree. Sixteen of the type I patients received only specific serum therapy, while thirteen received nonspecific serum therapy. Of the latter, five received only nonspecific serum therapy, eight, for whom pneumococcic type determination was completed before the end of forty-eight hours of illness, were given nonspecific therapy and were then observed long enough to judge of its complete effect, when they were given specific serum therapy. Certain characteristics of the two groups of cases which indicate that they were of similar severity are listed in table 1. They were similar in respect to the average duration of the

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6 (a) Neufeld, F, and Haendel, L. Weitere Untersuchungen über Pneumokokken-heilsera. III Mitteilung. Ueber Vorkommen und Bedeutung atypischer Varietäten des Pneumokokkus, *Archiv für Gesamte Medizin* **34** 293, 1910. (b) Cecil, R. L., and Blake, F. G. Studies on Experimental Pneumonia. VII. Treatment of Experimental Pneumococcus Type I Pneumonia in Monkeys with Type I Antipneumococcus Serum, *J. Exper. Med.* **32** 1, 1920. (c) Goodner, Kenneth. Further Experiments with the Intradermal Pneumococcus Infection in Rabbits, *J. Exper. Med.* **48** 413, 1928.

7 Howard, Campbell P. The Diagnosis and Treatment of Pneumonia, Oxford Monographs on Diagnosis and Treatment, New York, Oxford University Press, 1931, vol. 10.

8 Sutliff, W. D., and Finland, M. Type I Lobar Pneumonia Treated with Concentrated Pneumococcic Antibody (Felton), *J. A. M. A.* **96** 1465 (May 2) 1931.

disease before admission to the hospital, the incidence of positive blood cultures and the development of complications, but the patients who received only specific serum therapy had a slightly higher average age owing to the inclusion of two patients of more than 50 years of age and showed a greater incidence of alcoholism. Two patients in each group died.

Two varieties of nonspecific concentrated horse serum were used. One was prepared from antimeningococcic serums by the antitoxin and vaccine laboratory of the Massachusetts Department of Public Health and furnished through the courtesy of Dr. Benjamin White. The second was a concentrated solution of normal horse serum globulin, which was prepared and furnished through the courtesy of Dr. L. D. Felton of the department of preventive medicine and hygiene, Harvard Medical School. Type-specific concentrated antipneumococcic serums were furnished by the antitoxin and vaccine laboratory of the Massachusetts Department of Public Health. The methods of preparation were, in each case, those used in the concentration of antipneumococcic serum as described by Felton,<sup>9</sup> with the exception of a lot of antipneumococcic serum and a lot of antimeningococcic serum that were concentrated according to the method of Goodner.<sup>10</sup> The protein content of the solutions of normal horse serum globulin,

TABLE 1—*Severity of Type I Lobar Pneumonia in Two Groups of Patients Receiving Different Therapy*

	Number of Patients	Average Duration on Admission, Hours	Positive Blood Cultures on Admission	Number with Empyema	Average Age, Years	Number of Cases with Chronic Alcoholism
Specific therapy	16	55	8	1	34.5	7
Nonspecific therapy	13*	54	7	1	30.0	2

\* Includes the eight patients subsequently given specific therapy.

calculated from the nitrogen content, varied from 39 mg. to 84 mg. per cubic centimeter, of the antimeningococcic serum globulin, from 54 mg. to 82 mg. per cubic centimeter, and of the antipneumococcic serum globulin, from 76 mg. to 100 mg. per cubic centimeter.

The globulin from normal horse serum was administered to four patients, and the globulin from antimeningococcic serum was administered to nine patients, with similar results. The nonspecific serums tended to produce immediate circulatory and respiratory symptoms which, while transitory and apparently harmless, were occasionally severe. The symptoms were flushing of the face, dyspnea and a sense of compression of the chest. In only a single patient was there such an immediate reaction following the administration of specific therapy. Chills were also more frequent following the nonspecific serum, occurring in seven of thirteen cases, whereas they followed the use of antipneumococcic serum in only seven of twenty-four cases. Serum sickness of the delayed variety occurred in varying frequency according to the total amount of horse serum given—once in four recovered patients who received only nonspecific serum, three times in fourteen recovered patients who received specific serum, and five times in seven patients who received both specific and nonspecific serum.

<sup>9</sup> Felton, L. D. The Concentration of Antipneumococcus Serum, J. A. M. A. **94** 1893 (June 14) 1930.

<sup>10</sup> Goodner, Kenneth. Experiments on the Concentration of Antipneumococcic and Antimeningococcic Horse Serum. J. Immunol. **19** 473, 1930.

Dosage and methods of administration that have been successful in the administration of type I antipneumococcic serum in the past<sup>8</sup> were used. The nonspecific serum was given as nearly as possible according to the same plan as specific serum. An arbitrary total amount, thought to be sufficient for maximum clinical effect, was given in divided doses by means of dry, sterile syringes, intravenously at two hour intervals, beginning with 5 cc and increasing to 50 cc. The later in the course of the disease the treatment was begun, the more serum was considered necessary for symptomatic relief. A total of 30 cc was given to patients treated within the first twenty-four hours of the disease, and for each additional day of illness before treatment was begun this dose was increased by 30 cc. The total dosage of nonspecific serum tended to be lower than that of specific serum, because, when the same patient received both varieties of therapy, the specific serum was given later, and consequently in larger amount. Furthermore, in certain patients the calculated dosage of nonspecific serum was curtailed because of the occurrence of reactions. The dosage of the nonspecific serum varied from 32 to 178 cc, with an average of 71 cc, the specific serum, from 5 to 170 cc with an average of 112 cc, and the specific serum given to patients who had already had nonspecific serum, from 117 to 340 cc, with an average of 162 cc. With the exception of a patient who received only 5 cc of specific serum and who had what appeared to be a spontaneous crisis at about the time serum was begun, all the patients received at least 30 cc of each type of serum.

#### RESULTS

It has been shown<sup>8</sup> that in lobar pneumonia observation of the symptomatic response is a simple and straight-forward method of judging the effect of serum therapy. The duration of the acute disease, the presence and alterations in bacteremia and the occurrence of extensions of the consolidation in the lungs were studied in relation to the intravenous administration of solutions of horse serum globulin with and without specific antibodies. In comparing the duration of the disease in relation to therapy, only cases in which the patients recovered were considered. In the cases in which purulent complications or serum sickness developed it was possible in all but one patient, who received both nonspecific and specific serum, to recognize a symptom-free interval marking the end of the acute disease before the second febrile attack. The data for this patient were omitted from the comparative figures of the duration of the acute disease. The effects of treatment on the blood culture and on the extent of pulmonary involvement were compared in those who died as well as in those who recovered.

*Duration of the Disease*—Differences between the effect of non-specific and specific serum on the duration of the disease were noted in the first few patients treated. It was subsequently found possible to administer, first, nonspecific serum with only temporary effect and, later, specific serum with marked permanent response. An example of such a case is illustrated by the following case report.

## REPORT OF A CASE

*History*—The patient, H C, a married white woman, aged 36, was admitted on Dec 16, 1931. She complained of sudden chill, pain on the right side of the chest and fever twelve hours before admission to the hospital. The past history was irrelevant, except for a mild chronic cough of many years' duration, with asthma in the winter, influenza and pneumonia fourteen years before admission and dry pleurisy in the left side of the "chest" one month before the present writing. She was five months pregnant.

The initial chill lasted about two hours. Generalized pains, headache, weakness, nausea and vomiting appeared.

*Physical Examination*—The patient was acutely ill and in great pain, she was dyspneic and breathed rapidly. Her teeth were carious, the right tonsil was hypertrophied. Signs of consolidation were present over the lower lobe of the right lung. A loud friction rub was present in the right axilla. The patient's sputum was moderate in amount, despite the frequent coughing, and was glairy and mucoid in appearance.

*Laboratory Findings*—The urine contained a slight trace of albumin. Blood counts on the day after admission showed 3,700,000 red corpuscles and 27,500 white corpuscles per cubic millimeter. The patient's sputum at this time was found to contain type I pneumococcus. Blood cultures showed no growth on the first day of illness, pneumococcus type I, on the third day and no growth on the fifth day.

*Roentgen Examination*—Central consolidation of the lower lobe of the right lung was found.

*Treatment and Course*—Thirty hours after the onset of the illness antimeningococcic serum therapy was begun, and 74 cc was administered within seven hours. Reactions occurred after each dose of serum, characterized by mild nausea and dyspnea, and a chill after each of the two doses of 30 cc. The temperature fell from 103 to 98 F, the pulse rate, from 120 to 90 beats a minute, and the respiratory rate, from 40 to 25 a minute. The temperature and pulse rate returned to 104 F and 135 beats a minute, respectively, within twenty-four hours after the last dose of nonspecific serum. The blood culture, which had been negative on admission to the hospital, showed *Pneumococcus*, type I, at that time. Specific antipneumococcic serum therapy was begun, and 102 cc was given in the course of twenty hours. Immediate reactions similar to those that occurred after the nonspecific serum were observed. The temperature returned to normal after the administration of 43 cc of specific serum, and a permanent subjective change for the better, with relief of acute symptoms, such as dyspnea, pleural pain, marked cough and vomiting, occurred. A blood culture taken two days later, or four days after illness began, was negative. Mild serum sickness, characterized by fleeting pains in the joints and urticaria, appeared on the fifth and sixth days after the last dose of serum. Convalescence was uneventful.

This case history illustrates the dosage of serum given to patients receiving both nonspecific and specific therapy. Chart 1 shows the data for this case and also demonstrates the method of analyzing the duration of the acute disease in relation to the temperature curve. The first sustained drop of the temperature (*C*) was chosen as the point at which the temperature fell below, and later remained below, 101 F. Complete symptomatic improvement (*D*) implied that the temperature remained below 100 F, and that all symptoms of the acute disease were absent.



The most significant observation in this case was that while a temporary symptomatic improvement occurred following the administration of nonspecific serum, a marked and permanent change occurred following specific therapy. The marked contrast between the temporary symptomatic effect of nonspecific serum and the lasting effect of specific anti-pneumococcic serum was observed with greater or less clarity in all of the seven patients in whom the comparison was made.

The duration of the illness in relation to the administration of non-specific or specific serum in the patients who recovered is shown in charts 2 and 3. Since the duration of the disease at the time therapy is begun modifies the effectiveness of specific therapy, it is necessary to compare patients treated in the same stage of the disease. For this

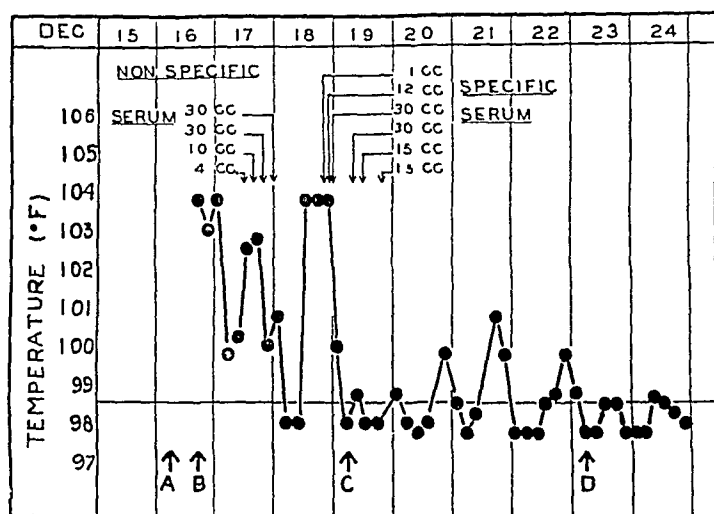


Fig 1—Temperature chart of patient H. C., who had type I lobar pneumonia, indicating dosage of serum and duration of disease. A, onset of pneumonia, B, entrance to hospital, C, first sustained drop in temperature, and D, complete symptomatic improvement.

purpose there were available thirteen patients who recovered and received only specific therapy and ten patients who recovered and received nonspecific therapy during the first four days of the disease. In seven of the latter patients the duration of the disease was modified by the subsequent administration of specific serum, but the contrast between the duration of the disease in the two groups is still marked. The relationship of the administration of serum to the first sustained sharp drop in temperature is indicated in chart 2. The duration of the disease up to the appearance of complete symptomatic improvement is shown in chart 3. The marked and regular effect of specific therapy in shortening the acute disease and the lack of effect of nonspecific therapy are indicated in both of these charts. The patients who received only specific therapy showed a cessation of the acute symptoms of the



hours for patients specifically treated and one hundred and eighteen hours for those nonspecifically treated. This contrast is also evinced by the fact that the average duration up to the disappearance of all acute symptoms was one hundred and thirty-seven hours for those specifically treated and two hundred and eighty hours for those nonspecifically treated. It seems probable that had no specific therapy been subsequently given to seven of the patients treated with antimeningococcic horse serum globulin, the average duration of the condition in the patients nonspecifically treated would have been still longer.

#### BACTEREMIA

No effect of specific therapy in lobar pneumonia has been more striking than that exerted on the bacteremia. The patients treated here showed a fairly high incidence of bacteremia, which was similar in the

TABLE 2—*Results of Therapy*

Blood Culture Before Therapy	Blood Culture After Therapy					
	Nonspecific Therapy			Specific Therapy		
	Number of Patients	Number Negative	Number Positive	Number of Patients	Number Negative	Number Positive
Positive	7	2	5*	11	10†	0
Negative	6	3	3	13	9‡	0

\* One patient had a temporary negative blood culture after nonspecific therapy.

† One patient had no blood culture made after therapy.

‡ Four patients had no blood culture made after specific therapy, in one because of early death and in three because of recovery.

two groups. The effect of therapy is summarized in table 2. The nonspecific globulin solution had no effect on bacteremia comparable to that of the specific serum, which in every case permanently removed the bacteria from the blood. In patients who had no bacteremia before treatment, organisms later appeared in the blood in three of the patients nonspecifically treated, but did not appear in the blood of any patients specifically treated. It is worthy of note that pneumococci disappeared from the blood in three of the patients receiving nonspecific serum, in two permanently, and in one for only a few hours. The same phenomenon has been observed occasionally in this hospital following the intravenous administration of dextrose solution, and is known to occur temporarily after transfusions of blood. It is possible that this was a mere coincidence, as bacteremias undergo fluctuations that are unassociated with therapy, but the further possibility that nonspecific injections may have a regular but temporary effect in lowering the bacterial content of the blood as has been shown by Goodner<sup>6c</sup> in rabbits, must be borne in mind.

## EXTENSION OF THE PULMONARY CONSOLIDATION

A spread of the pneumonic lesion that was sufficiently marked to be confirmed by roentgen examination was sought in every case as an indication of prognosis and of the effectiveness of therapy. In none of the patients receiving specific therapy was a spread observed but in five of the thirteen patients receiving nonspecific therapy such an extension was seen.

## COMMENT

Previous studies of antipneumococcic serum therapy have been controlled by the simultaneous observation of patients who received no intravenous injections. The control patients whose cases are reported here were given solutions of horse serum globulin intravenously that were similar to antipneumococcic serum, except for the absence of type-specific antibodies, and the symptomatic effects achieved by the two different therapeutic materials were so consistent that the study of even a small series provided adequate data for comparison. A control was thus provided for the nonspecific actions which follow the use of specific antipneumococcic serum, but which cannot otherwise be separated from the specific effects for purposes of observation. Comparisons were made not only in different patients, but also in the same patients. They indicate that the significant symptomatic effects of serum therapy in type I lobar pneumonia depend on the presence of type-specific antibodies.

There were, however, certain symptomatic changes that followed the intravenous administration of the horse globulin that did not contain antibodies, namely, a sensation of well-being, a drop in temperature, sometimes critical in degree and abruptness, a fall in pulse rate and an occasional disappearance of bacteremia. All these changes were of short duration.

A review of previous observations on nonspecific protein therapy of lobar pneumonia shows that the symptomatic benefits are most frequently described in terms that suggest the temporary effects mentioned. Miller<sup>1</sup> reported the results of the treatment of fifteen patients with typhoid vaccine intravenously, noted three cases in which treatment led to a termination of the acute disease and observed temporary benefit in a number of other cases. Hiss and Zinsser,<sup>11</sup> in eight patients treated with leukocyte extracts, reported temporary symptomatic benefit, which was ascribed to nonspecific protein effects. Halleimann and Kahler,<sup>3</sup> using normal horse serum and von den Velden,<sup>2</sup> using normal human

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11 Hiss, P. H., and Zinsser, Hans. Experimental and Clinical Studies on the Curative Action of Leukocyte Extracts in Infections, *J. M. Research* **14**: 321, 1908.

serum and other serums containing small amounts of antipneumococcic antibodies, noted temporary effects in a small series of cases

From what is now known of the need for potent homologous serums administered intravenously in large doses, it seems probable that many of the early attempts at specific serum treatment were more nonspecific than specific. From the work of Klemperer,<sup>12</sup> in 1892, to that of Neufeld and Haendel,<sup>13</sup> in 1910, which called attention to the different types of pneumococci, antipneumococcic serums of unknown type and of unmeasured potency were used. Goldsborough,<sup>14</sup> writing in 1902, lists sixty-three authors who treated a total of 486 patients. While many of these authors used small doses and administered the serum intramuscularly, some gave doses as high as 20 cc intravenously. Temporary symptomatic effects were frequently mentioned. Later authors, who appreciated the importance of securing potent specific serum and administering large amounts intravenously, frequently did not determine the type of infection, and consequently treated many patients nonspecifically. Weitz,<sup>15</sup> Reuss,<sup>16</sup> Géronne,<sup>17</sup> Sonnenfeld<sup>1</sup> and Lichtenstein<sup>5</sup> have thus reported on patients treated with type-specific serum, prepared according to the directions of Neufeld and Haendel. Another group of untyped cases, in which the patients were treated with antipneumococcic serums furnished by the Pasteur Institute, have been reported by Weill-Hallé, Weissman-Netter and Aris,<sup>18</sup> d'Oelsnitz, Duplay and Carcopino,<sup>19</sup> Courcoux and Deglaire,<sup>20</sup> Etienne and Braun.<sup>21</sup>

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12 Klemperer, G. Kritischer Bericht über Zwanzig Fälle spezifisch behandelter Pneumonie, *Wien med Wchnschr* **42** 882, 1892

13 Neufeld, F., and Handel, L. Ueber Herstellung und Prüfung von Antipneumokokkenserum und über die Aussichten einer spezifischen Behandlung der Pneumonie, *Ztschr f Immunitätsforsch u exper Therap* **3** 159, 1909

14 Goldsborough, Brice W. A Contribution to the Treatment of Pneumonia with Antipneumococcic Serum, *J A M A* **38** 1681 (June 28) 1902

15 Weitz, W. Ueber die Behandlung der Pneumonie mit intravenösen Injektionen des Neufeld-Handelschen Pneumokokkenserums, *Med Klin* **8** 1072, 1912

16 Reuss, A. Beiträge zur Behandlung der Pneumonie mit dem Neufeld-Handelschen Pneumokokkenserum, *Deutsche med Wchnschr* **40** 1104, 1914

17 Géronne, A. Die Behandlung der Pneumonie mit dem Neufeld-Handelschen Pneumokokkenserum, *Berl klin Wchnschr* **49** 1699, 1912

18 Weill-Hallé, B., Weissman-Netter, R., and Aris, P. Pneumonies et broncho-pneumonies des vieillards, traitées par le serum antipneumococcique, *Bull et mem Soc med d hôp de Paris* **46** 227, 1922

19 d'Oelsnitz, Duplay and Carcopino. La serotherapie des pneumopathies aiguës, *Bull et mem Soc med d hôp de Paris* **46** 588, 1922

20 Courcoux and Deglaire. Traitement des pneumopathies aiguës à pneumocoques par la serotherapie, *Bull et mem Soc med d hôp de Paris* **46** 248, 1922

21 Etienne, G., and Braun, M. Serothérapie antipneumococcique, *Bull et mem Soc med d hôp de Paris* **47** 1813, 1923

and Lassance<sup>22</sup> The majority of these authors have felt that some temporary relief was obtained, and many described the sense of well-being and the drop in temperature and pulse rate as marking a temporary symptomatic change

Such temporary symptomatic effects have been presented as evidence of a definite therapeutic action of serum injections in lobar pneumonia It is apparent that they were similar to the nonspecific effects seen in the cases reported in this paper A number of the authors mentioned felt that the death rates in their series of cases were lower than the general death rate from the disease, but owing to the lack of an adequate control mortality rate and to the small number of patients treated, these statements are open to question The proportion of fatalities observed in "alternate case" controlled series of cases of pneumonia, as reported by Cecil and Sutliff<sup>23</sup> and by Finland,<sup>24</sup> indicates that in addition to the non-type-specific symptomatic effect there may exist a non-type-specific curative action of horse serum, since the fatality rate of pneumonia due to group IV pneumococci was less among patients who received serum containing antibodies for types I and II than among those who did not receive serum This reduction in mortality, which was not so great as the reduction in mortality in cases of type I pneumonia reported by the same authors, was not observed by Park, Bullowa and Rosenbluth,<sup>25</sup> who reported the treatment of a comparable series of cases The failure of the attempt reported in this paper to produce permanent symptomatic effects by means of nonspecific therapy in type I pneumonia would seem to indicate that the curative action of nonspecific therapy in the two series of cases of group IV cases just referred to might be questioned It is possible that cross-protective antibodies are sometimes present<sup>26</sup> for organisms of the miscellaneous group IV, or that errors were made in typing of the pneumococcus which tended to the inclusion of an occasional organism of type I or II in the heterogeneous group IV<sup>27</sup>

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22 Lassance, V Le traitement de la pneumonie par le serum antipneumococcique, *Presse med* **27** 30, 1919

23 Cecil, R L, and Sutliff, W D The Treatment of Lobar Pneumonia with Concentrated Antipneumococcus Serum, *J A M A* **91** 2035 (Dec 29) 1928

24 Finland, M The Serum Treatment of Lobar Pneumonia, *New England J Med* **202** 1244, 1930

25 Park, W H, Bullowa, J G M, and Rosenbluth, M B The Treatment of Lobar Pneumonia with Refined Specific Antibacterial Serum, *J A M A* **91** 1503 (Nov 17) 1928

26 Kolchin, Betty S, and Gross, Louis Observations on the Cross-Protective Power of Antipneumococcus Monovalent Sera, Types I, II, and III, *J Immunol* **9** 505, 1924

27 Sutliff, W D An Investigation of the Reliability of Sputum Typing for Pneumococcus by Mouse Method, *J Infect Dis* **42** 485 (May) 1928

The mechanism of the action of nonspecific therapy has been discussed by Petersen,<sup>28</sup> by Zinsser,<sup>29</sup> and by Weichardt<sup>30</sup> The changes that have been observed to occur following the parenteral injection of foreign protein are widespread in the body They consist of changes in the circulating antibodies, a shift of leukocytes to the splanchnic region together with a reciprocal dilatation and contraction between the cutaneous and the splanchnic capillaries, increased permeability of the capillaries, increased flow of lymph and changes in blood serum proteins, fibrinogen and enzymes Changes in the local inflamed area, such as dilatation of the capillaries, with resulting increased blood flow and freer exchange of antibodies and of toxic products between the lesion and the circulation also occur These effects are all temporary and variable They probably account together or separately for the temporary symptomatic changes that were noted in the nonspecific treatment in the cases here reported

#### SUMMARY

A comparison has been made between the symptomatic effects obtained in early type I lobar pneumonia by the administration of concentrated type-specific antipneumococcic serum and of horse serum globulin solution containing no specific antipneumococcic antibodies Both preparations were prepared and administered in the same manner

In eight patients who received, first, nonspecific and, later, specific therapy, the greater effectiveness of the latter was obvious

In thirteen specifically treated patients who recovered the duration of the disease was shorter than in the ten nonspecifically treated patients who recovered

Bacteremia was not present after therapy in any of the sixteen specifically treated patients, but bacteremia remained present in five, appeared for the first time in three and disappeared in two of thirteen nonspecifically treated patients

An extension of the consolidation of the lung was not observed after therapy in any of the sixteen specifically treated patients, but extensions were observed in five of thirteen patients receiving nonspecific therapy

A temporary symptomatic change was observed in each of the patients receiving nonspecific therapy, but the improvement in patients receiving specific therapy was permanent in every instance

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28 Petersen, W F Protein Therapy and Non-Specific Resistance, New York, The Macmillan Company, 1922

29 Zinsser, Hans Resistance to Infectious Disease, ed 4, New York, The Macmillan Company, 1931, p 470

30 Weichardt, W Unspezifische Immunisierung, in Kolle, W, Kraus, R, und Uhlenhuth, P Handbuch der pathogenen Mikroorganismen, ed 3, Jena, Gustav Fischer, 1931, vol 1, p 1147

# NEPHRITIC ALBUMINURIA

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Since the time of Bright, albuminuria has commonly been associated with disease of the kidneys. More recently the distinction has been made between non-nephritic and nephritic albuminuria. The former is most readily attributed to a transient and reversible increase in permeability of the glomerular membrane from partial asphyxia brought about by circulatory changes<sup>1</sup>. From time to time, however, the suggestion has been made that nephritic albuminuria is the result of changes in the plasma proteins rather than any change in or damage to the kidney itself. Epstein<sup>2</sup> saw in the albuminuria of nephrosis a disturbance of plasma protein formation, Kollert and Starlinger<sup>3</sup> an increased tissue destruction leading to increase in fibrinogen, and Munk and his associates,<sup>4</sup> an abnormality in the physicochemical state of the plasma colloids. The conception of extrarenal albuminuria is supported by the appearance of foreign proteins, such as egg albumin, in the urine after ingestion of large quantities, or after their intravenous injection. The albuminuria following the injection of foreign protein, however, is usually transitory and without evidence of lasting damage to the kidneys. Hamburger<sup>5</sup> found that with repeated injections of egg white the albuminuria decreases and even disappears, the kidney cells having become immune to the foreign protein. Garnier and Schulmann<sup>6</sup> have made similar observations.

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From the Department of Medicine of the Western Reserve University and Lakeside Hospital

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6 Garnier, M., and Schulmann, E. Sur l'albuminurie déterminée par l'injection de blanc d'oeuf au lapin, *Compt rend Soc de biol* **93** 600 (July 25) 1925



Andrews, Thomas and Welker<sup>7</sup> have suggested that albuminuria may be regarded as a method of detoxication of the body. Their conception is that a disturbance in the ratios of inorganic salts in the body allows proteins to escape from tissue cells which are foreign to the blood stream and are therefore excreted by the kidney, either alone or in combination with the plasma proteins, which because of such combination are themselves changed to foreign proteins. If such were the case, it seemed to us that plasma from nephritic patients who were excreting large amounts of protein should, when injected into a normal person, lead to the appearance of albuminuria.

We have, therefore, injected from 50 to 190 cc of citrated plasma from three such patients who had negative Wassermann reactions and no history or evidence of syphilis, into persons of compatible blood groups who had no albuminuria or detectable renal damage. In no case was albuminuria produced. Brief histories of the cases follow.

#### REPORT OF CASES

CASE 1—The clinical diagnosis was chronic nephritis with edema. The pathologic diagnosis four months later (Dr H T Karsner) was borderline case, no clearcut anatomic distinction between arteriolar nephrosclerosis and chronic nephritis.<sup>8</sup>

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<sup>7</sup> Andrews, E. Experimental Uremia, *Arch Int Med* **40** 548 (Oct) 1927. Andrews, E, and Thomas, W A. The Origin of Urinary Proteins, *J A M A* **90** 539 (Feb 18) 1928. Andrews, E, Thomas, W A, and Welker, W F. Albuminuria in the Mechanism of Detoxification, *Arch Int Med* **43** 139 (Jan) 1929.

<sup>8</sup> The kidneys grossly showed no distinct reduction in size but slight pitting of the surface. They were principally the seat of passive hyperemia. Microscopically, the capsule was absent. The surface showed numerous areas of depression at the base of which was a triangular area of fibrosis with lymphoid cell infiltration. The elevated portions showed small cystlike dilatations of the tubules. The connective tissue generally was slightly increased in amount and moderately edematous. The tubular epithelium and the subcapsular epithelium showed advanced cloudy swelling. Fat stains showed well marked fatty degeneration in both situations. Polarizing prisms failed to disclose anisotropic droplets. A few hyaline casts were present. The large and medium-sized arteries showed moderate intimal fibrosis. The small arteries showed marked intimal and medial fibrosis with only slight fatty changes. The arterioles in some places showed thick and fibrotic walls, but with only slight fatty changes. The glomeruli varied greatly in size, but those that were not markedly fibrotic were unusually large. Fibrosis attacked both the capsule and the tuft, and in numerous instances there was complete replacement of glomeruli by fibrous and fibrohyaline material. The larger tufts showed well marked lobulation and many blood-containing loops, appeared to be richly cellular and often showed adhesions between the tuft and the capsule. Variable degrees of fibrosis with slight hyaline change were found in the tufts, and occasionally a loop was completely hyalinized. The Azan-Carmine stain of McGregor showed considerable thickening of the basement membrane with only a few areas in which it was wrinkled. There were, then, severe chronic

E R, a Hungarian woman, aged 54, was admitted to the hospital on June 9, 1930, complaining of swelling of the legs and abdomen of nine months' duration, and of the arms and trunk for one month. Physical examination revealed no dyspnea, but marked pallor. There were marked sclerosis of the retinal arteries, many hemorrhages and patches of exudate. The lungs were normal except for a few râles at the bases. The heart was enlarged, the blood pressure was 230 systolic and 130 diastolic, falling to 170 systolic and 90 diastolic with rest. There was marked peripheral arteriosclerosis. The abdomen contained a moderate amount of fluid. The liver was not demonstrably enlarged. There were marked edema of the legs, and less of the arms and trunks. The volume of urine secreted was from 300 to 900 cc a day, the specific gravity was from 1.020 to 1.032, the protein content was from 2 to 9 Gm daily computed by Esbach's method, three estimations of protein nitrogen by Kjeldahl's method showed 6.4, 8 and 8.4 Gm, there were many hyaline and granular casts, and no red cells. The blood count showed 4,000,000 erythrocytes, hemoglobin, 60 per cent (Sahli), and 8,000 leukocytes. The blood urea nitrogen was 15 mg, creatinine 1.6 mg and cholesterol 240 mg, per hundred cubic centimeters. The total plasma proteins were 4.3 Gm per hundred cubic centimeters. The Wassermann test was negative.

On August 2, 100 cc of blood was drawn into a flask containing 10 cc of 2 per cent sodium citrate, the plasma was separated under sterile precautions, and 50 cc was injected intravenously into a healthy subject. There were no symptoms or reaction of any kind. Each specimen of urine voided by the recipient during the following twenty-four hours was tested qualitatively for protein with heat and acetic acid and with nitric acid. None gave a detectable reaction.

#### CASE 2—The diagnosis was subacute nephritis

L L, a 17 year old Negress, was admitted to the hospital on Nov 16, 1931, complaining of swelling of the face and ankles of five months' duration. Physical examination gave essentially normal results, except for edema of the lower lids and pitting edema of the ankles and legs and over the sacrum. The volume of urine was from 600 to 2,100 cc a day, the specific gravity was from 1.014 to 1.030, the albumin (Shevky and Stafford's<sup>9</sup> method) was from 6.7 to 7.3 Gm a day, there were a moderate number of erythrocytes and many hyaline and granular casts. The blood count showed 4,700,000 erythrocytes, 65 per cent hemoglobin (Sahli), 7,800 leukocytes. The test for phenolsulphonphthalein showed 60 per cent. The blood urea nitrogen was 12 mg per hundred cubic centimeters. The total plasma proteins were 5.3 Gm per hundred cubic centimeters. The Wassermann test was negative. Roentgen examination showed clouding of both antrums.

On January 2, 300 cc of blood was drawn into a flask containing 30 cc of 2 per cent sodium citrate. The plasma was separated under sterile precautions and 190 cc was injected intravenously into a healthy man whose blood showed no cross-agglutination with that of the patient. Thirty minutes after the injection urticarial wheals developed which were relieved by epinephrine. The recipient's urine showed no protein by qualitative test either before or after injection, nor could any increase in excretion of protein be detected by Shevky and Stafford's

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arterial and moderate arteriolar lesions, glomerular changes that were somewhat more like those of inflammatory than like those of arteriolar disease and a marked simple nephrotic component evident in the advanced cloudy swelling and fatty degeneration of the tubules.

<sup>9</sup> Shevky, M C, and Stafford, D D. A Clinical Method for the Estimation of Protein in Urine and Other Body Fluids, Arch Int Med **32** 222 (Aug) 1923

quantitative method either in the specimen voided an hour after injection or in those obtained during the following forty-eight hours

CASE 3—The diagnosis was chronic nephrosis

J T, a white man, 21 years of age, was admitted to the hospital on May 26, 1932, complaining of generalized edema and swelling of the abdomen of six months' duration. Physical examination showed marked pallor and generalized edema involving particularly the legs, the lower part of the trunk and the scrotum. The eyegrounds were normal, the lungs were apparently normal. The heart was not enlarged to percussion, the blood pressure was 130 systolic and 90 diastolic, the peripheral vessels were soft. The abdomen contained a moderate amount of fluid. The volume of urine was from 450 to 1,400 cc a day, the specific gravity was from 1.014 to 1.038, the albumin was from 19 to 33.3 Gm a day (Shevky and Stafford's method). The sediment showed many hyaline and granular casts and no red cells on ordinary examination. An Addis count showed red cells 616,000, white and epithelial cells, 53,000,000, and casts, 20,000,000, per twelve hours. There was 25 per cent excretion of phenolsulphonphthalein after intravenous injection. The blood urea nitrogen was 27.6 and the cholesterol, 477 mg per hundred cubic centimeters. The total plasma protein was 4.3 mg. The blood count showed 4,000,000 erythrocytes, 80 per cent hemoglobin and 9,400 leukocytes. The basal metabolism rate was —13 per cent. The Wassermann test was negative.

On May 25, 400 cc of blood was drawn into a flask containing 40 cc of 2 per cent sodium citrate, the plasma separated under sterile precautions and 175 cc injected intravenously into a healthy man whose blood showed no cross-agglutination with that of the patient. There was no reaction of any kind. The recipient's urine gave no qualitative test for protein before or after injection. By Shevky and Stafford's method, the concentration of protein in the recipient's urine for twenty-four hours before injection was approximately 0.006 mg per hundred cubic centimeters, for the twenty-four hours after injection, it was the same.

The question naturally arises whether the amount of plasma injected contained enough foreign protein to be detectable even if it were excreted. This is difficult to answer definitively. In case 3, the daily protein in the urine was usually in excess of 20 Gm. Assuming the plasma volume to be 5 per cent of the body weight (73 Kg), the total plasma volume would be about 3.65 Kg, or approximately 3,360 cc. The total plasma proteins were 4.3 per cent making a total of about 145 Gm in the blood stream. The patient was thus excreting the equivalent of about one seventh of his total plasma proteins a day. If a similar ratio is assumed for the plasma transfused, about 1 Gm of the 7.53 Gm of protein injected would have been excreted if it had stayed in the patient's vessels. The method used for detecting protein could easily be read to 0.015 mg per hundred cubic centimeters (or about 0.15 Gm in a twenty-four hour volume of urine). Therefore, if one sixty-seventh of the protein excreted by the patient, or one five hundredth of the plasma proteins injected, represented foreign proteins, we believe that we could have detected it, provided all of it were promptly eliminated by the kidney. If the excretion took place slowly during twenty-four hours, about one fiftieth of the protein injected would have to have been excreted in order to be readily detected.

These experiments may be regarded as another failure to demonstrate by direct experiment qualitative changes in the plasma proteins of persons having nephritic albuminuria. It is well established that intravenous injection of sufficient foreign protein may be followed by albuminuria, the urinary protein containing both the foreign protein and serum proteins. The amount of foreign protein excreted, however, is always less than that injected,<sup>10</sup> and albuminuria when it occurs, is most readily explained by a toxic damage to glomeruli, for by no means is every intravenous injection or liberation of foreign protein in the blood stream followed by albuminuria, even when definite systemic reactions are produced. We have failed to detect protein in the urine of four patients receiving intravenous injections of from 25 000 000 to 1,600 000,000 typhoid bacilli, although in each case there was a well marked reaction characterized by chill and fever, nor have we detected it with any regularity after the chills of therapeutically induced malaria.

These experiments are consonant with the dialysis experiments of del Baere<sup>11</sup> and Gaebler<sup>12</sup> who failed to find any increased diffusibility of the plasma proteins of patients with albuminuria and are contrary to those of Andrews, Thomas and Welker.<sup>7</sup> A similar experiment was reported by Rusznyak and Nemeth,<sup>13</sup> who did not find any greater proteinuria when a dog's kidney was perfused with diluted serum from a patient with nephrosis than when normal serum was used, and concluded that albuminuria is due to alterations in the glomeruli, not in the plasma proteins. After a detailed discussion of the extrarenal factors in albuminuria, Volhard<sup>14</sup> concluded that "in the last analysis every albuminuria must be attributed to damage of the kidney epithelium."

#### CONCLUSION

Intravenous injection of plasma from three patients with nephritis who were excreting large amounts of protein did not cause albuminuria in healthy recipients. This is regarded as inconsistent with the conception that nephritic albuminuria is due to the presence of foreign toxic proteins in the blood stream.

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10 Schmid, J. Ueber den Ausscheidungsort von Eiweiss in der Niere, *Arch f exper Path u Pharmakol* **53**:419, 1905

11 del Baere, L. J. Die Ursache der Albuminurie bei der Nephrose, *Ztschr f d ges exper Med* **79** 743, 1931

12 Gaebler O. H. Diffusibility of the Proteins of Normal and Pathological Plasma, *J Biol Chem* **93** 467 (Oct) 1931

13 Rusznyak, S., and Nemeth, L. Die Entstehung der Albuminurie, *Ztschr f d ges exper Med* **70**:464, 1930

14 Volhard, F. Nieren und ableitende Harnwege, in von Bergmann, G., and Staehelin, R. *Handbuch der inneren Medizin*, ed 2, Berlin Julius Springer, 1931, vol 6, p 821

# SPONTANEOUS SUBARACHNOID HEMORRHAGE

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WHEELING, W VA

Despite characteristic and striking clinical symptoms and a not infrequent occurrence, the syndrome of spontaneous subarachnoid hemorrhage is still largely unrecognized in general practice. This fact, together with the recent observation of a case of spontaneous subarachnoid hemorrhage, has prompted a brief review of the present status of the subject and a report of the case at hand.

Subarachnoid hemorrhage, like jaundice or puritus, is merely a symptomatic expression of some more fundamental pathologic state. Subarachnoid hemorrhage as a coincidental sign may be found in a variety of pathologic conditions. It may occur in trauma directed to the skull or vertebral column, as in fracture or dislocation, when vessels are ruptured and blood is extravasated into the subarachnoid space. It may occur in acute or chronic inflammatory processes in the meninges or encephalon, as in meningococcic, syphilitic or tuberculous meningitides or in epidemic and hemorrhagic encephalitides (vaccinia, smallpox and measles). Its occurrence has been reported in dyscrasias of the blood, such as purpura, hemophilia, scurvy and the leukemias, in which a defect in the factors of coagulation exists. Subarachnoid hemorrhage has been known to occur in such miscellaneous states as pernicious anemia, polycythemia, sickle cell anemia, Korsakoff's psychosis, migraine and vascular neurosyphilis and as a sequel to the administration of serums or vaccines. The rupture of cerebral cysts or the erosion of blood vessels by cerebral neoplasms affords other causes of subarachnoid hemorrhage. Hypertension, whether permanent, as in chronic nephritis, or transient, as in the paroxysms of eclampsia, epilepsy or pertussis, is a fruitful source of subarachnoid hemorrhage. Toxins, such as lead and alcohol, may initiate hemorrhage from the cerebral vessels into the subarachnoid reservoir.

The type of subarachnoid hemorrhage in which all the aforementioned factors, whether traumatic, infectious, toxic, neoplastic, hypertensive or dyscrasic, can be excluded as causative has been termed "spontaneous." The term "spontaneous" has been well chosen, because the hemorrhage usually makes its appearance suddenly and dramatically, without evident cause, in a person previously in apparently vigorous health. The term "spontaneous" is perhaps applied in this connection

in the same sense that it is applied in "spontaneous combustion" in the realm of chemistry. Again, the expression "spontaneous" is in no sense to be regarded as equivalent to that equivocal term "idiopathic," because in each instance of spontaneous subarachnoid hemorrhage there is a definite pathologic process. This pathologic process always consists of disease or degeneration of the cerebrospinal arteries per se.

The usual cause of spontaneous subarachnoid hemorrhage is the rupture of a congenital aneurysm or an aneurysm resulting from a congenital defect in the vessel wall. Symonds, Ohler and Hurwitz,<sup>1</sup> McIver and Wilson,<sup>2</sup> and Fearnside have supported this view. The last named investigator reported forty-four cases of aneurysm of the cerebral arteries among 5,432 patients on whom autopsy was performed at the Pathological Institute of London Hospital between the years 1907 and 1913, of this number, the condition in thirty-one cases was due to medial degeneration and in thirteen, to embolic processes. Such aneurysms most frequently involve branches of the circle of Willis at their bifurcation and may be single or multiple.

Strangely enough, syphilis is practically never a cause of cerebral aneurysm, and hence it is not a cause of spontaneous subarachnoid hemorrhage. Fearnside has shown that while syphilis causes 96.2 per cent of aortic aneurysms and practically all aneurysms of other vessels, it is rarely a cause of intracranial aneurysm. In the cerebral arteries syphilis causes obliterating endarteritis, but not aneurysms. Ohler and Hurwitz<sup>1</sup> recently reported twenty-four cases of spinal subarachnoid hemorrhage in all of which the Wassermann tests of the blood and spinal fluid were negative.

Aside from aneurysm, a few other causes of intrinsic cerebral vascular disease have produced spontaneous subarachnoid hemorrhage. Transverse rents in the internal elastic lamina of the blood vessels have been found on microscopic study. Cerebral arteriosclerosis is an occasional cause. Functional vasomotor disturbance of the cerebral vessels with extravasation of blood has been suggested in a few instances.

Symonds has rightly stated that the blood present in the spinal fluid must have its origin from one of four sources: (1) the rupture of a vessel lying in the subarachnoid space, (2) hemorrhage from a superficial cerebral vessel, with rupture through the pia mater into the subarachnoid, (3) hemorrhage from a deep cerebral vessel into the ventricles and finally (4) rupture from a subdural vein through the subarachnoid membrane.

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<sup>1</sup> Ohler, W. R., and Hurwitz, D. Spontaneous Subarachnoid Hemorrhage, *J. A. M. A.* **93** 1856 (May 28) 1932.

<sup>2</sup> Wilson, G., and McIver, J. Spontaneous Subarachnoid Hemorrhage, *J. A. M. A.* **93** 89 (July 13) 1929.

## HISTORICAL REVIEW

It is interesting to note from the historical point of view that spontaneous subarachnoid hemorrhage was not recognized clinically earlier than 1904. Prior to that time, diagnoses were made only post mortem. While Sir William Gull, in 1859, discussed the possibility of aneurysmal rupture as the cause of subarachnoid hemorrhage, Wilks in the same year actually reported four cases. Gentree collected thirty-four cases from the literature in 1869. Froin, in 1904, by accurately describing the characteristics of admixtures of blood and spinal fluid, and Quincke, in 1891, by his invention of the lumbar puncture, established criteria and methods by means of which a diagnosis could be made ante mortem. Samuel Leopold<sup>3</sup> was one of the earliest investigators of the subject in American medical literature; he published an article on spontaneous leptomeningeal hemorrhage in *The Journal of the American Medical Association* in 1914.<sup>4</sup> Both he and Josephine Neal (1926) decried the paucity of American reports as compared with the relative frequency of cases in English, Swedish and French medical literature. Feinsides, in 1916, recognized the cause of spontaneous subarachnoid hemorrhage as being a rupture of a congenital aneurysm in the young or arteriosclerotic degeneration in the aged. By 1924, C. P. Symonds of Guy's Hospital had collected seventy-seven references from the literature, only one case of which was from an American source. Since 1929, however, an increasing number of American investigators have reported cases, among them McIver and Wilson<sup>2</sup> (July 1929) who reported fifteen cases, Smith<sup>5</sup> (June, 1930), Leopold<sup>3</sup> (January 1930) who reported three cases, Sands<sup>6</sup> (July, 1930), and, finally, Ohler and Hurwitz,<sup>1</sup> who recorded twenty-four cases of this syndrome (May 28 1932).

The incidence of spontaneous subarachnoid hemorrhage may be gaged by the statement of Ohler and Hurwitz that it constitutes one fifteenth of all cerebrovascular accidents and is equivalent in frequency to a better recognized clinical entity—subacute bacterial endocarditis. They reported twenty-four cases of spontaneous subarachnoid hemorrhage occurring at the Boston City Hospital in the eighteen months elapsing between June, 1929, and January, 1931. On the other hand,

3 Leopold, S. S. Spontaneous Subarachnoid Hemorrhage, *M. Clin. North America* **13** 869 (Jan.) 1930.

4 Leopold, S. Subarachnoid Hemorrhage, *J. A. M. A.* **63** 1363 (Oct. 17) 1914.

5 Smith, W. A. Spontaneous Subarachnoid Hemorrhage, *South. M. J.* **23** 494 (June) 1930.

6 Sands, J. Subarachnoid Hemorrhage as a Clinical Complication of Neurosyphilis, *Arch. Neurol. & Psychiat.* **24** 85 (July) 1930.

S S Leopold reported only three cases on the medical service of the University of Pennsylvania in the year 1929

The onset of symptoms of spontaneous subarachnoid hemorrhage is sudden, dramatic and brutal. Almost universally patients at the onset have been engaged in exertion, such as running, playing games, laughing or coughing. The case reported is the only one in the literature available to me which occurred coincidentally with the strain of intercourse. The patients frequently have been in good health and are in the fourth or fifth decade of life. The average age was only 27 years in Neal's cases and 30 years in Symonds' but in the twenty-four cases of Ohler and Hurwitz it was 50 years (the youngest being 17 years, the oldest 75 years)

The first and indeed the only symptom complained of may be violent and excruciating occipital headache of such abrupt onset that the patient may feel as if he had been "struck at the base of his skull." This headache may be associated with severe suboccipital pain. Vertigo and persistent vomiting are next most frequent symptoms. Coma or stupor may be present in larger hemorrhages. Some disorientation or mental confusion, somnolence or slowness of comprehension may coexist with the pain in the head if coma does not supervene.

Moderate elevation of temperature to between 99 and 102 F is the rule. The highest elevation occurs the first week, when the greatest hemolysis and pigment absorption are present. Defervescence may require from ten to twelve days. Referred pains along the peripheral nerves may occasion herpes zoster or sciatic neuralgia. Objectively, very little neurologic or physical disturbance may be present. There are two fairly constant signs, a stiff, rigid neck and a positive Kernig sign. Paresis of the facial muscles or of one or more extremities may exist, the reflexes are not infrequently abolished, although they may be present or hyperactive. Pupillary findings are variable. Subretinal hemorrhages from effusion of blood along the optic nerve sheaths and choked disks have been recorded.

From the laboratory standpoint, a leukocytosis of 13,000 or 14,000 is often present. A trace of albumin or even of dextrose may occasionally be found in the urine.

A spinal fluid uniformly mixed with blood and under increased tension is a requisite finding. The blood must be present equally in three or more consecutive test tubes, it should not clot and there should be xanthochromia of the supernatant spinal fluid for three or four hours after the accident, becoming progressively deeper the first week and ultimately clearing up in patients who recover. These criteria serve to eliminate the finding of blood in the spinal fluid from extraneous accidental sources.



The following case report is classic

#### REPORT OF A CASE

*History*—E W, a white man, aged 40, a postmaster by occupation, who had previously been in excellent health, was seen at the Glendale Hospital in consultation with Dr Covert of Moundsville, on May 27, 1932. The patient's chief complaints were violent occipital headache and dull lumbar backache. The headache had had an abrupt, catastrophic onset at 4 p m, Sunday, May 23, 1932, immediately after the successful performance of conjugal coitus. At the termination of the act, the patient had felt a snap in the occipital area of his head and thought that he had dislocated a vertebra, so intense was the ensuing pain. The pain or ache in the head was situated in the occipital area, it was excruciating and was referred anteriorly to each temporal area. With each heart beat, the patient had felt a paroxysmal intensification of the pain. The headache was not relieved by any of the usual measures and continued largely unabated for two days, when he was removed to the hospital. Only two measures had temporarily alleviated the pain in the head—a full warm tub bath had given relief, for half an hour, and elevation of the head had aided a trifle.

There had been no tinnitus aurium, vertigo or symptoms relative to the cranial nerves. The patient had not vomited. There had been no period of unconsciousness. However, the patient was somewhat disoriented when seen, his comprehension was dulled.

Two days after the onset, marked stiffness of the neck with actual soreness of the suboccipital muscles developed. At the same time, a dull, constant, lumbosacral backache appeared. Pains were also referred down the posterior aspects of both thighs along the course of each sciatic nerve.

The patient's past illnesses were insignificant. No history of a recent cold in the head, injury or acute infection was obtained. He had last consulted a physician eighteen months previously, and then only for a routine insurance examination. He had been feeling quite well for several years and had gained 25 pounds (11.3 Kg) in the past four years. He said that he had not had venereal infection. The patient had been married twice. The family history was essentially unimportant.

*Examination*—Complete physical and neurologic examinations revealed a surprising lack of findings. The only positive findings were (1) marked rigidity of the neck and soreness of the suboccipital muscles, (2) a bilaterally positive Kernig sign and (3) elicitation of slight pain along the course of the sciatic nerves in their crural extent and soreness of the posterior crural muscles.

The patient was a large, well built, slightly obese man of hypersthenic and plethoric habitus. He was obviously worried and had an anxious expression on his face. His complexion was ruddy. He was slightly confused. The blood pressure was 110 systolic and 65 diastolic, there was no evident peripheral or retinal arteriosclerosis. The temperature was 101 F, the pulse rate was 88 a minute. The head was of normal configuration and presented no pathologic deviations. The pupils were somewhat small, but they were regular and equal and responded well to light and in accommodation, and the convergence was normal. The auditory canals and ear drums were normal, and nasal inspection gave negative results. The teeth were in good condition, the tonsils were normal and the sinuses clear on transillumination. There was no evidence of a pulmonary, pleural or cardiac pathologic condition. Abdominal, rectal and genital examinations gave negative results.

The gait was essentially normal. There was slight swaying in the Romberg position. No defect in the cranial nerves, the sensory modalities or the superficial or deep tendon reflexes was present. Cerebellar signs were absent. No abnormal associated or involuntary movements or anomalies in motor strength or muscle status were in evidence.

Lumbar puncture revealed a uniformly bloody spinal fluid under an increased pressure of 260 mm of water. The blood was equally distributed in each of four tubes and did not clot. The red cells formed a sediment in each tube, and the supernatant fluid was xanthochromic. Other examinations of the spinal fluid gave the following data:

- 1 The cell count showed 32 leukocytes.
- 2 A differential count of leukocytes revealed 20 lymphocytes, or 62.5 per cent, and 12 polymorphonuclears or 37.5 per cent.
- 3 The Pandy and Ross-Jones tests showed an increased amount of globulin.
- 4 The colloidal gold test was negative.
- 5 The Wassermann test was negative in dilutions of 0.2, 0.4 and 0.6 cc.
- 6 Smears were repeatedly found to be negative.
- 7 Cultures were repeatedly negative.
- 8 A quantitative test for sugar showed 48 mg per hundred cubic centimeters.
- 9 A quantitative test for protein showed 60 mg per hundred cubic centimeters.

The Wassermann and Kahn tests of the blood were negative on May 27, 1932. A typical blood count made on May 27, 1932, showed 9,800 leukocytes, with 79 per cent neutrophils, 17 per cent small lymphocytes, 2 per cent large lymphocytes and 2 per cent eosinophils. The red cell count and hemoglobin were normal. Repeated urinalyses showed no unusual observations, there were traces of indican, a slight amount of acid, a specific gravity of from 1.004 to 1.012, no sugar, no albumin, an occasional hyaline cast in one specimen, a trace of acetone in another, amorphous urates and uric acid crystals.

*Course*—The patient's treatment was pursued along the following lines:

- 1 A lumbar puncture was made daily, with the removal of from 20 to 30 cc of sanguineous fluid. During the first week the supernatant fluid became progressively saffron yellow, then gradually the fluid began to lose its pigment, until by the twelfth day it was practically clear. The punctures were continued until the fluid was clear and under normal tension. The punctures were the most effective single measure in relieving the pain in the head.

- 2 Daily intravenous injections of 500 cc of a hypertonic 10 per cent solution of dextrose were made.

- 3 A saline catharsis was administered each morning.

- 4 Complete rest in bed with the continuous application of two ice caps to the head was given.

- 5 Mild analgesics were used.

The patient remained in the hospital for two weeks. His convalescence was uneventful after the first week, when the headache, backache and fever largely subsided. He was discharged on June 9, 1932, free from symptoms. He has now returned to his former work and apparently enjoys his usual health.

#### COMMENT AND CONCLUSION

The abrupt onset of the pain was doubtless due to the rupture of a congenital aneurysm, situated perhaps along a posterior branch of the basally placed circle of Willis. With each ventricular systole a paroxysmal intensification of the pain ensued from increased extravasation of

blood into the subarachnoid space. All of the symptoms were due to two factors (1) the increased intracranial pressure and (2) the extravasation of blood into a closed serous sac. Meningeal irritation would account for the stiff neck and the bilateral Kernig sign. The irritation of the sacral roots of the sciatic nerve, which pursue a long intrathecal course, by the blood pigment would serve to explain sacral backache and sciatic neuralgia. Finally, it must be noted that while the patient is apparently well, another aneurysmal rupture may ensue.

# ORAL ADMINISTRATION OF IRON IN HYPOCHROMIC ANEMIA

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One of the oldest problems in which modern scientific medicine has interested itself is that concerning the efficacy of iron in the treatment of anemia. Perhaps no other problem has attracted so much thought and work with results so little in agreement. This idea has been expressed well by Whipple and Robscheit-Robbins <sup>1</sup> "The history of anemia treatment with drugs is indeed a tale to make the judicious grieve."

Some of the conflicting ideas regarding iron medication may be traced to the careless application of the discoveries made in experimental anemia in animals to the anemias that occur in man. For the present, until more is known of the mechanisms involved in different types of anemia, in man and animals, the statement of Witts is much to the point, namely, that no apology is needed for considering the field of clinical medicine the testing ground of iron therapy <sup>2</sup>

In the past hundred years the prescribed dose of iron in anemia has varied widely. Blaud, in 1832,<sup>3</sup> soon after he had announced the efficacy of certain pills which he regarded as specific in the treatment of chlorosis, voiced an objection to a formula which reduced the strength of his pills to about one-half. On the whole, not only since that time, but since at least the time of Sydenham, iron was considered of great value in the treatment of chlorosis <sup>4</sup>. In the hands of those physicians who found it specific in this disease it was used in large doses for prolonged periods. During that century iron was often prescribed in doses that today would be considered too small. For a period in recent years it has been relegated to a minor therapeutic position, chiefly by reason of its lack of effect experimentally in acute blood loss, possibly

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School

1 Whipple, G. H., and Robscheit-Robbins, F. S. Blood Regeneration in Severe Anemia. III. Iron Reaction Favorable, *Am J Physiol* **72** 419, 1925

2 Witts, L. J. Discussion on the Therapeutic Uses of Iron, *Proc Roy Soc Med* **24** 543, 1931

3 Blaud, P. Pilules anti-chlorotiques, *Bull gén de thérap* **2** 154, 1832

4 Christian, H. A. A Sketch of the History of the Treatment of Chlorosis with Iron, *M Lib & Hist J* **1** 176, 1903

also because of the less frequent occurrence of severe chlorosis and because of its frequent use in anemia that cannot respond to iron therapy. Recently it has been elevated once again to a position of great importance in the treatment of certain kinds of anemia. This extraordinary change in the point of view has been commented on by Whipple and Robscheit-Robbins<sup>1</sup>

The different kinds of iron preparations that have been employed are as various as the different dosages recommended. In general, the activity of different iron preparations is believed to depend on the physical and chemical state of the iron which they contain<sup>5</sup> and on the gross amount of iron which is given in the daily dose<sup>6</sup>. Organic iron preparations are not as effective as inorganic preparations<sup>7</sup>. Reimann and Fritsch<sup>8</sup> found that ferrous chloride and ferrous sulphate in small doses were much more active in producing hemoglobin regeneration than the corresponding ferric salts.

Much further research is necessary before it is learned what is the best form of inorganic iron preparation to employ clinically. There are numerous simple preparations which are potent in types of cases that are known to respond to iron, if they are given in the proper dosage and for an appropriate length of time. An analysis of the important factors in eighty-four cases of hypochromic anemia due to various causes is the basis of the present report.

#### METHODS

As a rule, venous blood was taken every other day for complete blood studies. The percentage of reticulocytes was determined daily on capillary blood during the first few weeks of treatment. Subsequently, when the hemoglobin reached a level of over 60 per cent of normal and the patient had left the hospital, the hemoglobin and the number of red blood corpuscles were determined at about monthly intervals.

The hemoglobin was determined by the Sahli hemometer, which had been standardized by determinations of the oxygen capacity of the blood by the Van Slyke apparatus. One hundred per cent hemoglobin was taken as the equivalent of 15.6 Gm. per hundred cubic centimeters of blood, or 21 per cent by volume of oxygen capacity. The blood counts were made with United States Bureau of

<sup>5</sup> Morawitz, P. Ueber Eisen- und Arsenpräparate, München med. Wchnschr. **71** 1266, 1924.

<sup>6</sup> (a) Mettier, S. R., and Minot, G. R. The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastrointestinal Contents in Certain Cases of Anemia, *Am. J. M. Sc.* **181** 25, 1931. (b) Keefer, C. S., Huang, K. K., and Yang, C. S. Liver Extract, Liver Ash and Iron in the Treatment of Anemia, *J. Clin. Investigation* **9** 533, 1930.

<sup>7</sup> Elvehjem, C. A. The Relative Value of Inorganic and Organic Iron in Hemoglobin Formation, *J. A. M. A.* **98** 1047 (March 26) 1932.

<sup>8</sup> Reimann, F., and Fritsch, F. Vergleichende Untersuchungen zur therapeutischen Wirksamkeit der Eisenverbindungen bei den sekundären Anämien, *Ztschr. f. klin. Med.* **115** 13, 1930.

Standards' pipettes and counting chambers For the determination of the reticulocytes, smears of capillary blood were stained supravitaly with brilliant cresyl blue, dried, counterstained with Wright's stain and mounted permanently after the methods of Hawes<sup>9</sup> and Cunningham<sup>10</sup>

Iron was administered by mouth in the form of iron and ammonium citrate (brown scales) or pills of ferrous carbonate, U S P, and in a few instances other preparations of inorganic iron were used Metallic iron in iron and ammonium citrate is about 17 per cent, that is, in each gram of the salt there is about 170 of metallic iron In each pill of ferrous carbonate there is approximately 30 mg of metallic iron These values were used in estimating the dosage and its effects in individual cases

#### CLINICAL MATERIAL

Eighty-four patients with hypochromic anemia, who responded well to iron, are under consideration here (table 1) They have been chosen

TABLE 1—*Classification of Eighty-Four Cases of Hypochromic Anemia Responding to Iron*

Chief Etiologic Factors	Number of Cases	Percentage
Idiopathic hypochromic anemia with achlorhydria or hypochlorhydria	33	39
Chronic blood loss	35	42
Inadequate diet	10	12
Recent pregnancy and inadequate diet	2	7
Carcinoma of stomach and chronic blood loss	2	
Hodgkin's disease and chronic blood loss	1	
Amebic dysentery and chronic blood loss	1	
Total	84	100

from a large group of patients with different forms of anemia who have been carefully studied in this clinic during the past four years Selection of the cases for the present study has been based arbitrarily on either at least a 1 per cent rise of hemoglobin per day and satisfactory clinical improvement following iron, or the absence of a type of anemia that cannot respond to iron and that has severe complications which experience has shown might hinder the effect of iron Many of the cases had multiple etiology, for example, poor diet associated with a chronic loss of blood from peptic ulcer, or idiopathic hypochromic anemia with achlorhydria with chronic menorrhagia No hypochromic pregnancy anemias which respond to iron are included, although there are a few cases of anemia in women in whom a previously terminated pregnancy had undoubtedly contributed to the anemia There are also included two cases of cancer of the stomach with achlorhydria, one of Hodg-

9 Hawes, J B A Study of the Reticulated Red Blood Corpuscles by Means of Vital Staining Methods Its Relation to Polychromatophilia and Stippling, Boston M & S J **161** 493, 1909

10 Cunningham, T D A Method for Permanent Staining of Reticulated Red Cells, Arch Int Med **26** 405 (Oct) 1920

kin's disease and one of amebic dysentery, in all of which there had been a pronounced chronic loss of blood

In the selection of suitable cases, it is important to exclude cases of anemia due primarily to severe infections, cancer, nephritis and certain other causes, because such complications hinder the action of iron in hypochromic anemia just as they hinder the effect of potent material in pernicious anemia<sup>11</sup> Many of the eighty-four patients had such complications to a minor degree, but as a rule not sufficiently to hinder greatly the action of the iron medication

Table 2 gives an additional list of forty-two cases of anemia of various etiologies in which large amounts of iron had been given and no response or a small response obtained The majority of the patients had color indexes of 1 or more Slight responses to iron were obtained

TABLE 2—*Classification of Forty-Two Cases of Anemia in Which Adequate Trial with Iron Gave no Response or Only a Small Response*

Chief Etiologic Factors	Number of Cases
Cancer (stomach, large bowel, pancreas, metastatic)	6
Sepsis (pyelitis, cystitis, pneumonia, tuberculosis, abscess)	9
Chronic nephritis	4
Megalocytic anemia of unknown origin (including aplastic anemia)	5
Myelogenous leukemia	5
Scurvy	4
Hemolytic jaundice	3
Myxedema	1
Cirrhosis of the liver	2
Total number of cases	42

in only a few of the forty-two cases, and the color indexes were below 1 The patients with megalocytic anemia of unknown origin, leukemia, scurvy and hemolytic jaundice had color indexes above 1 and gave absolutely no response to iron In addition to these cases, eight normal persons showed no response while taking between 0.3 and 2 Gm of iron daily in the form of ferrous carbonate or iron and ammonium citrate Mention should also be made of a group of patients with pernicious anemia in whom, during the response of the blood to liver extract or some other potent material, hypochromic anemia developed, they then responded to iron

#### FACTORS NECESSARY IN ACCURATE CLINICAL INVESTIGATION OF THE EFFECTS OF IRON THERAPY

Early experiments of Whipple on the acute loss of blood in dogs seemed to lead to the conclusion that iron was of no value in the treat-

<sup>11</sup> Minot, G. R., and Castle, W. B. The Adequate Treatment of Anemia, *Ann Int Med* 5: 159, 1931

ment of anemia The experiments of Williamson and Ets<sup>12</sup> seemed to lead to the same conclusion Whipple's subsequent experiments showed that iron could be of considerable value in long-standing severe anemia in which by prolonged severe bleeding and diet control the stores of hemoglobin-building material were reduced until regeneration was much slowed down This process, which requires so long and is so difficult to produce in the dog, can take place frequently and apparently rather easily in man This possibility was not recognized formerly, and because iron seemed to fail in so many kinds of anemia, it was thought by many to be useless in all kinds

Ten years ago, Meulengracht<sup>13</sup> reviewed the difficulties of judging the effectiveness of iron in different kinds of anemia and the necessity of adequate control periods At that time he was not aware of the value

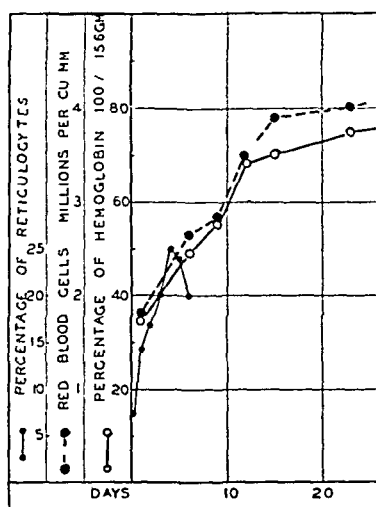


Chart 1—The blood changes in a man with acute hematemesis from peptic ulcer, apparently having adequate stores of blood-building material The response of the reticulocytes, red blood cells and hemoglobin to the acute blood loss was good, without the administration of iron, except after the fifteenth day

of the reticulocyte reaction, but now, since the value of determining the effectiveness of iron by this prompt reaction has been shown, a portion of the difficulties has been overcome In the clinical investigation of iron therapy in hypochromic anemia there are two factors of primary importance first, the selection of suitable cases, and second, the establishment of adequate control periods

Charts 1, 2 and 3, which are illustrative of these facts, represent the blood findings in three men, each of whom entered the hospital with loss of blood from peptic ulcer Chart 1 represents the blood findings in a

12 Williamson, C S, and Ets, H N The Value of Iron in Anemia, Arch Int Med **36** 333 (Sept) 1925

13 Meulengracht, E Large Doses of Iron in the Different Kinds of Anaemia in a Medical Department Acta med Scandinav **58** 594, 1923



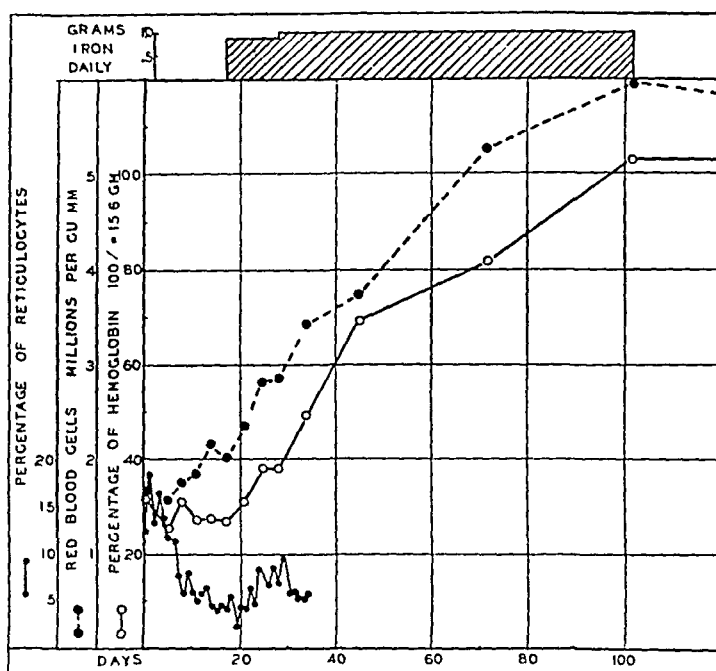


Chart 2—The blood changes in a man with acute hematemesis from peptic ulcer, apparently having inadequate stores of blood-building material. There was a response of the reticulocytes and red blood cells, but the hemoglobin did not rise until after iron was administered. Note the development of a color index below 1.

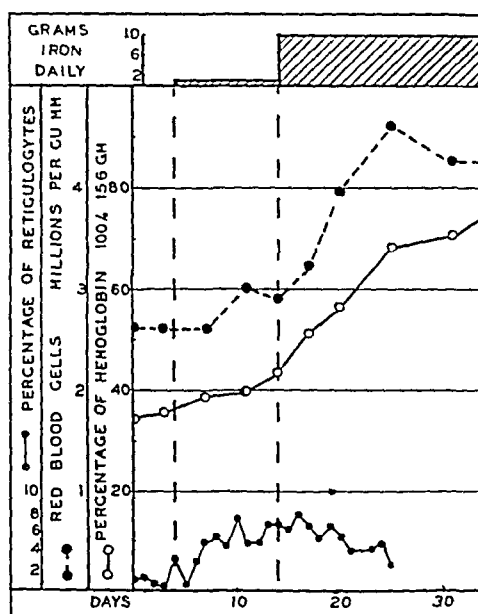


Chart 3—The blood changes in a man with previous chronic blood loss from peptic ulcer. The stores of blood-building material had apparently been reduced, and the color index was below 1. A response of reticulocytes, hemoglobin and red blood cells occurred following the administration of 0.1 Gm of iron. Note the more rapid response of the hemoglobin and red blood cells after the administration of 1 Gm of metallic iron daily.

man who had acute hematemesis and showed marked anemia when he entered the hospital. The color index was 1, there was a pronounced response of reticulocytes to the loss of blood and a prompt rise of both hemoglobin and red blood cells. He required no iron to produce this response, and iron probably would have caused his blood to rise no faster. He apparently had a good hemoglobin-building reserve to meet the emergency. As recovery took place the color index began to decrease, and it is possible that iron at this later time would have hastened the return of the hemoglobin to normal. Chart 2 represents a similar situation, but an inability to meet the emergency, so that in spite of a high reticulocyte rise due to a loss of blood there were only a slow rise of red blood cells, no rise of hemoglobin and a lowering of the color index. The hemoglobin-building reserve was apparently low, and the administration of iron was of benefit, as shown by the reticulocyte response and the abrupt rise of hemoglobin and red blood cells and the rising color index. Chart 3 shows the blood findings of a man who had a history of a chronic loss of blood from duodenal ulcer. The color index was low, and there was very little evidence of any regenerative ability on the part of the bone marrow. A daily dose of 100 mg. of iron was somewhat effective, but a daily dose of 1 Gm. of iron produced a further reticulocyte response and caused the hemoglobin to rise faster. It must be emphasized that patients were on diets composed almost entirely of milk and cream. These patients were, therefore, from a hematologic point of view, somewhat similar to Whipple's dogs at various stages of bleeding.

The necessity for adequate control periods is well brought out by these cases. It is clear that anemia due to an acute loss of blood is unsuitable for the demonstration of the effectiveness of iron therapy. On the other hand, an acute loss of blood coming after a prolonged period of chronic loss of blood, poor diet or some other condition favoring anemia, such as achlorhydria, may provide an excellent opportunity for testing the blood-building power of iron preparations. In other words, to demonstrate the potency of a preparation of iron in a patient with hypochromic anemia, there must be a sufficient reduction in the patient's reserve of hemoglobin-building material to render him unable to manufacture more than a maintenance amount of hemoglobin.

There are various mechanisms that may produce such a deficiency if one takes into consideration the different types of hypochromic anemia which are known to respond to iron. These may be divided into four main classes: (1) chronic loss of blood, (2) dietary deficiency, (3) gastro-intestinal disorders, and (4) pregnancy. It is obvious that the store of hemoglobin-building material may be reduced by a loss of blood. A diet restricted especially in green vegetables, fruit and meat affords an insufficient supply of such material. Gastro-intestinal dis-

orders may interfere with the proper assimilation of this material in the food, as, for example, in the anemia associated with chronic dysentery<sup>14</sup> This is also well exemplified by the type of anemia known as idiopathic hypochromic anemia with achlorhydria in which the absence of hydrochloric acid in the stomach is associated with an apparent inability to utilize hemoglobin-building substance in the food<sup>6a</sup> In pregnancy the transfer of hemoglobin-building material from the mother to the fetus explains in part, at least, the frequent production of an iron-responding anemia in the mother, while a change in the secretory ability of the stomach of the mother during pregnancy probably also plays a part<sup>15</sup> The rôle played by altered gastric function in the production of hypochromic anemia is of such great importance that it must be evaluated in any case even if some other cause for anemia is present

#### THE DETERMINATION OF OPTIMAL IRON DOSAGE

Of course, iron dosage has been optimal if the blood response is rapid and if the patient makes satisfactory clinical improvement, but to reach a more definite conception of the appropriate dose certain objective facts are needed Two kinds of tests have been used in order to approach this conclusion the first is an arbitrary test, the second, a comparative test For the arbitrary test the response of the reticulocytes and the rate of hemoglobin rise after iron were compared to certain standards and expressed in terms of percentage of those standards For the comparative test the response of the reticulocytes and the hemoglobin after a small daily dose of iron for from eight to twelve days was compared to the response after a larger daily dose for a similar period of time The arbitrary test as employed in the eighty-four cases responding well to iron will be discussed first

*The Arbitrary Test*—The standard for the response of the reticulocytes to iron has been taken from data given by Minot and Heath<sup>16</sup> and is shown in chart 4 Since the height of the reticulocyte rise after iron in hypochromic anemia is inversely proportional to the level of the red blood cells and hemoglobin, considered together, before treatment, the expected height of the reticulocyte rise may be determined for each case by referring to chart 4 This may be done best by averaging the

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14 Keefer, C S, Yang, C S, and Huang, K K Anemia Associated with Chronic Dysentery, *Arch Int Med* **47** 436 (March) 1931

15 Strauss, M B, and Castle, W B The Aetiology and Treatment of Anaemia in Pregnancy, *Lancet* **1** 1198, 1932 Strauss, M B Observations on the Etiology and Treatment of Anemia in Pregnancy, *J Clin Investigation* **11** 809, 1932

16 Minot, G R, and Heath, C W The Response of the Reticulocytes to Iron, *Am J M Sc* **183** 110, 1932

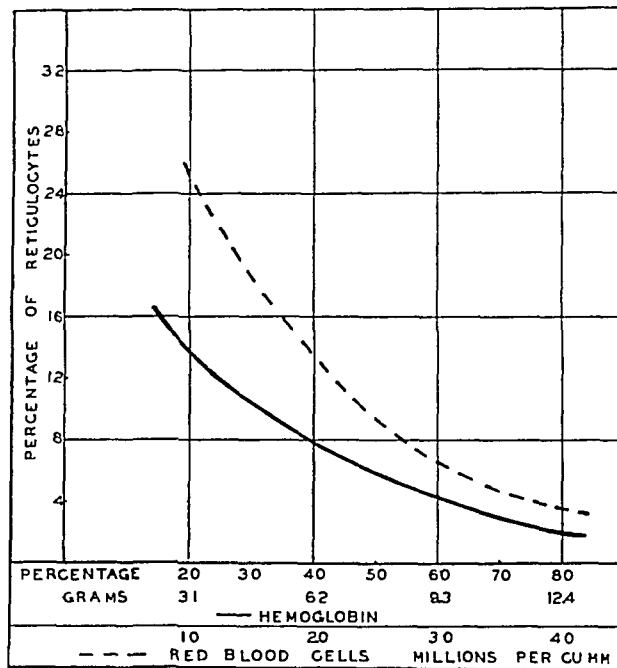


Chart 4—The average response of the reticulocytes at the peak of their rise in cases of hypochromic anemia responding to iron. The red blood cell and hemoglobin levels, before treatment with iron was started, are recorded as abscissae. Taken from data given by Minot and Heath (*Am J M Sc* **183** 110, 1932).

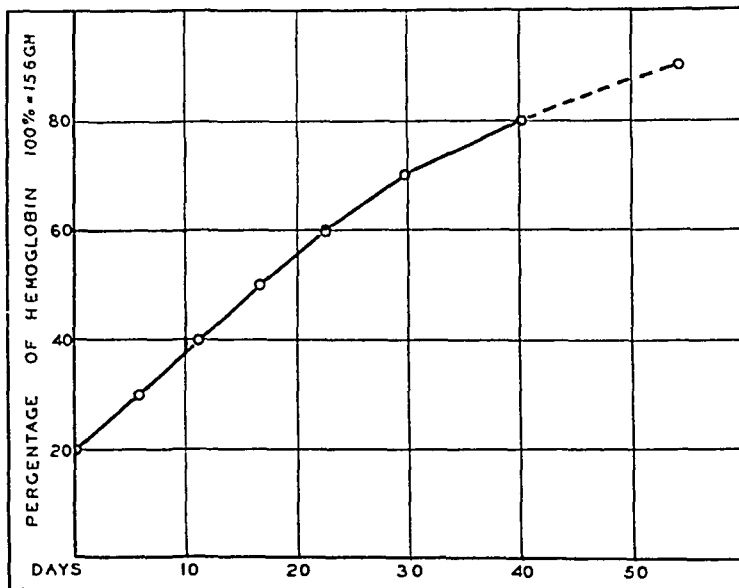


Chart 5—The average rate of hemoglobin increase in eighty cases of hypochromic anemia during the administration of iron.

percentage of the expected maximal reticulocyte rise at the initial red blood cell level and at the initial hemoglobin level

The standard for determining the expected rate of hemoglobin rise is shown in chart 5. This figure has been constructed as follows: Based on experience with more than two hundred cases, a rise of 1 per cent (0.16 Gm) of hemoglobin per day may be assumed to be the lower limit of a satisfactory rate when the initial hemoglobin is below 50 per cent (7.8 Gm). The number of days required for the hemoglobin to rise each 10 per cent when the rate was 1 per cent a day or faster was determined for each of eighty cases, according to the method described by Josephs.<sup>17</sup> The average was charted and is shown in chart 5. Rises in hemoglobin above 80 per cent occurred only in those patients who continued to improve steadily, whether or not the rate was 1 per cent per day. Therefore, the rate of hemoglobin rise above 80 per cent as expressed in chart 5 is optimal. It was the exception rather than the rule for the hemoglobin in an individual case to continue to rise throughout the entire course of improvement as evenly as the average which is shown in chart 5. In many cases there was considerable irregularity in the rate of hemoglobin increase. The curve for the average, however, compares well with that given by Josephs<sup>17</sup> for anemia in children responding to iron. When the hemoglobin is below 50 per cent, the rate is somewhat slower than that given by Josephs. Above this level it is faster and apparently corresponds more closely to his figures for the hemoglobin rise in children who received copper in addition to iron. This seems to contribute to the evidence that will be mentioned later that copper given in addition to iron in hypochromic anemia in adults does not have any definite influence.

The rate of hemoglobin rise in any given case during the administration of iron may be expressed in percentage of the expected rise as determined from chart 5. Thirty-four per cent of the eighty-four patients had hemoglobin rises due to iron therapy, which were satisfactory when judged by this method. Forty-six per cent had satisfactory reticulocyte rises when judged by the arbitrary test for the height of the reticulocyte rise after iron. The two tests are therefore fairly comparable, and they also afford a standard which requires of a case of hypochromic anemia rapid blood regeneration and therefore adequate iron dosage.

In judging the dosage of iron by this method, the average of the percentages of the expected reticulocyte rise and the expected hemoglobin rise was taken as the criterion. If the average was 100 per cent or over, the dosage arbitrarily was considered optimal; if below 100 per cent, the dosage was considered suboptimal.

<sup>17</sup> Josephs, H. Treatment of Anaemia of Infancy with Iron and Copper, *Bull. Johns Hopkins Hosp.* 49: 246, 1931.

In only about one half of the cases was there good correlation between the percentage of expected reticulocyte rise and the percentage of expected hemoglobin rise. The discrepancy shown by the remainder of the cases is probably due as much to the errors of the method as it is to the difference in the types of cases and variation in iron dosage. Occasionally in two similar cases there might be in one a low reticulocyte response and a high hemoglobin response and in the other, a low hemoglobin response and a high reticulocyte response. Cases in which the etiology of the anemia was different showed similar discrepancies. The explanation for this state of affairs has not been discovered, but it may be dependent on different reserve powers for the manufacture of cells and for the formation of hemoglobin or on some fundamentally different cellular state of the bone marrow.

After determining in this manner what doses of iron had been optimal, it was apparent at once that the optimal dose varied a great

TABLE 3—*Analysis of the Response to Iron in Thirty-Eight Cases of Hypochromic Anemia in which Patients Were Given 1 Gm of Metallic Iron as Iron and Ammonium Citrate Daily*

	Total Number of Cases	Number of Cases Having Complications	Number of Cases Having Reduced or Absent Free Hydrochloric Acid in the Stomach After Histamine
Response over 100 per cent of the standard	16	2	5
Response less than 100 per cent of the standard	22	8	11

deal from patient to patient. Thirty-four patients, as determined by the methods indicated, received an optimal dosage of iron, averaging 0.72 Gm daily. Fifty patients received a suboptimal dosage averaging 0.69 Gm daily. However, there was a general trend for the smaller doses to produce submaximal responses. For example, in 40 per cent of twenty-one cases in which a dose of from 0.35 to 1 Gm of metallic iron had been given daily, this dose was optimal, on the other hand, in only 19 per cent of twenty-six cases in which the dose was from 0.1 to 0.35 Gm daily was this quantity optimal.

When a dose of about 1 Gm of iron had been given and the response was submaximal in an individual case, there was often some complication, such as moderate sepsis with fever, that explained the unsatisfactory response. Many of the patients had idiopathic hypochromic anemia, a condition in which the absence of free hydrochloric acid in the stomach may interfere with the proper assimilation of iron.<sup>61</sup> This is well exemplified in the analysis of the responses of thirty-eight patients to whom iron and ammonium citrate, containing 1 Gm of metallic iron, was given daily (table 3). Of these patients, sixteen, or 42 per cent, had responses over 100 per cent of the standard which would indicate

that the dosage had been optimal, and of these sixteen patients, five had idiopathic hypochromic anemia, and two additional patients had complications. Twenty-two of the thirty-eight patients, or 58 per cent, had responses less than 100 per cent of the standard, indicating a suboptimal dosage, and of these, eleven patients had idiopathic hypochromic anemia, and eight additional patients had complications. The same results appear when groups of patients receiving a smaller dosage of iron and ammonium citrate and those receiving ferrous carbonate are analyzed in this manner.

In comparing the cases of nine patients who received pills of ferrous carbonate with those of sixty-nine patients who received iron and ammonium citrate, the data showed that a smaller average dose of iron in the form of ferrous carbonate gave greater responses than the larger average dose of iron in the form of iron and ammonium citrate. It is not believed that there is as much discrepancy in the effect of these two iron preparations as this statement would seem to indicate. Evidence will be given subsequently regarding this point.

A considerable difference could be demonstrated when the average response of the thirty-three patients with idiopathic hypochromic anemia was compared to that of the forty-one patients with a chronic loss of blood. The average daily dose of iron was about the same in the two groups of cases, namely, 0.7 Gm. of metallic iron. The average percentage response of the arbitrary standard was maximal in only 29 per cent of the thirty-three cases of idiopathic hypochromic anemia, whereas it was maximal in 53 per cent of the forty-one cases of chronic blood loss.

A detectable response of reticulocytes and hemoglobin was generally noted with small doses of iron (less than 0.1 Gm. of metallic iron daily). One patient, who had chronic blood loss from the uterus, was remarkable in that her blood responded maximally to only 85 mg. of metallic iron in the form of iron and ammonium citrate daily. On the other hand, the following dosages were demonstrated in three patients to be absolutely ineffective: 85, 50 and 60 mg. of metallic iron daily.

It would appear, therefore, that a dose of iron that is optimal for one case of hypochromic anemia may be suboptimal for another, but, in general, small doses of iron are likely to be suboptimal. When a large dose of iron (1 Gm. of metallic iron daily) is given and the response is submaximal there may be some complication. An optimal dose of iron in hypochromic anemia due to an uncomplicated chronic blood loss and without achlorhydria is probably a suboptimal dose in idiopathic hypochromic anemia with achlorhydria. These points are brought out perhaps more strongly in the study of individual cases, and will be further illustrated by the comparative test of iron dosage.

*The Comparative Test*—The comparative test is that which has been employed by various investigators in the comparison of the effect of several substances on the formation of blood. The test consists in the uniform daily administration of a substance (in this case a certain dose of iron), followed immediately by the uniform daily administration of a second substance (or a larger dose of iron). In this way any additional reticulocyte response and any faster rate of hemoglobin rise occurring during the administration of a larger dose of iron are quite conclusive of a more effective iron dosage. If no reticulocyte rise is obtained and the anemia is sufficient to permit one when a larger dose of iron is given, and if a response occurred when the first dose was given, the first dose of iron is presumably optimal. A similar state of

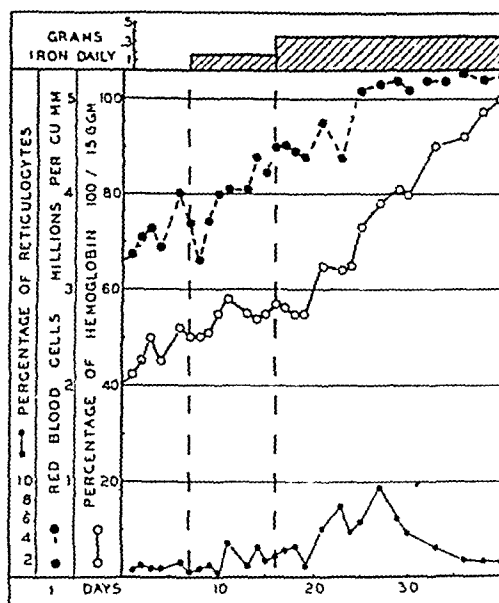


Chart 6—The blood changes in a case of hypochromic anemia following the daily administration of first 180 mg of metallic iron as iron and ammonium citrate and subsequently 360 mg. The latter dose was far more effective, as shown by the greater reticulocyte response and the increased rate of hemoglobin formation.

affairs holds for the rate of increase of hemoglobin, but one must judge the rate according to the initial hemoglobin level, for it often is faster at low hemoglobin levels than at high levels. This comparative test is similar to the method used by Reimann and Fritsch<sup>8</sup> for the demonstration of the superiority of ferrous salts over ferric salts, with the exception that the change between two doses is made abruptly without a period of rest between the doses. The test is illustrated in chart 6, in which 180 mg of metallic iron, as iron and ammonium citrate daily, produced a slight reticulocyte response and a hemoglobin rise, but 360 mg was far more effective. The response to the second dose was well over the maximal response, when judged by the arbitrary test, so that in this particular case there is good reason for thinking that 360 mg



of iron daily was optimal. Table 4 gives the results in all of the cases tested in this manner. It is seen from this table that doses as high as 0.76 Gm. of iron daily were suboptimal, whereas in several other cases smaller doses of iron than this were apparently optimal.

Data from a case of idiopathic hypochromic anemia are shown in chart 7, which illustrates by such a comparative test the fact that the same dose of an iron salt may be more effective if prepared in a particularly suitable form for assimilation. As is well known, pills of ferrous carbonate may be made too firm and with time may become

TABLE 4—Comparative Responses of Hypochromic Anemia to Different Doses of Iron (Ferric and Ammonium Citrate Unless Otherwise Indicated)

Etiologic Factors	Initial Dose, Gm. of Iron	Dose Which Gave Second Reticulocyte Response, Gm. of Iron	Dose Which Gave Faster Hemoglobin Rise, Gm. of Iron	Dose Which Did Not Give Faster Hemoglobin Rise, Gm. of Iron
Idiopathic hypochromic anemia, chronic blood loss	0.085	0.19	0.34	0.19
Restricted diet	0.09	0.18	0.18	
Chronic blood loss	0.18	0.36	0.36	
Idiopathic hypochromic anemia	0.19	0.85	0.51	
Idiopathic hypochromic anemia	0.17	1.00	1.00	
Chronic and acute blood loss	0.085	1.00	1.00	
Idiopathic hypochromic anemia, chronic blood loss	0.22		1.02	
Chronic and acute blood loss	0.34	1.02	1.02	
Idiopathic hypochromic anemia	0.17	1.00	1.00	
Idiopathic hypochromic anemia	0.21	1.00		1.00
Chronic blood loss	0.34			1.00
Idiopathic hypochromic anemia, chronic arthritis	0.085			1.00
Idiopathic hypochromic anemia	0.25			0.34
Chronic blood loss	0.76			1.00
Restricted diet	0.09*		0.35*	
Chronic blood loss	0.46*		0.96	
Amebic dysentery	0.35*		0.52*	
Restricted diet	0.06*			0.35*
Postpregnancy, acute blood loss	0.85†			2.60†

\* Ferrous carbonate

† Ferrum reductum

hard and resistant. If the preparation is powdered and administered in gelatin capsules, it is in a form more readily available for solution in the gastro-intestinal tract. As is shown in chart 7, the patient received the equivalent of 4 pills of ferrous carbonate (120 mg. of metallic iron) a day for ten days, to which she responded only slightly. When she was given the same number of pills after they had been powdered, a definite second reticulocyte response and a marked rise in the hemoglobin and red blood cells occurred. The equivalent amount of metallic iron given in the form of ferric sulphate and sodium bicarbonate caused no noticeable increased effect, whereas the equivalent amount of iron in the form of ferrous sulphate and sodium bicarbonate again produced a definite reticulocyte response. These two combinations of substances were given

with the intention of showing that the reduced form of pills of ferrous carbonate is more effective than the oxidized form (ferric carbonate). The latter form presumably is present to a large extent in pills that have been prepared a long time previous to use. A final moderate reticulocyte response occurred when iron and ammonium citrate in a larger daily dose (1 Gm of metallic iron) was given. This figure, then, shows how different preparations containing the same dose of iron may vary in their effectiveness and how a larger dose of iron may be more effective than a smaller dose.

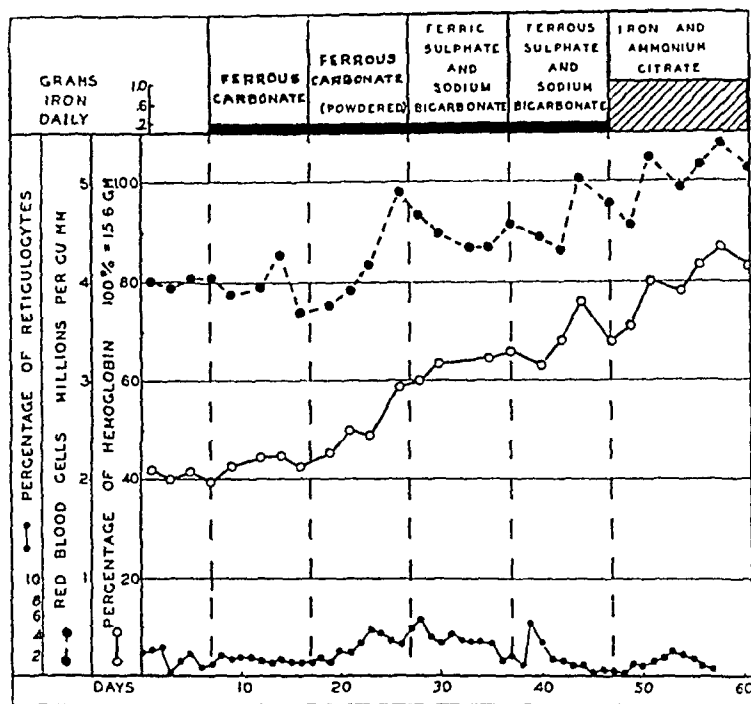


Chart 7—The blood changes in a case of hypochromic anemia during the administration of iron in different physical and chemical states. Note the lack of response to pills of ferrous carbonate given as such, and the excellent response to the same preparation given in powdered form. None of these preparations in a dose of 0.2 Gm of metallic iron was more effective than 1 Gm of metallic iron given daily in the form of iron and ammonium citrate.

#### THE UTILIZATION OF IRON ADMINISTERED ORALLY

It is well known that most of the iron administered orally leaves the body in the feces. To what extent the iron is absorbed or is reexcreted into the intestine is not known. However, the amount of iron contained in the newly formed hemoglobin may serve as an index of the iron retained by the body. This idea was adopted to arrive at a definite conclusion regarding the amount of iron that may have been absorbed and utilized in the building of hemoglobin in the cases studied. The percentage of utilization of iron was determined for each case. For this it is necessary to know the blood volume, which for the present purpose,

was assumed to be 5 liters for each subject. The grams of hemoglobin per hundred cubic centimeters of blood gained during the period of hemoglobin rise is therefore multiplied by 0.003, a convenient, average figure for the amount of iron in hemoglobin<sup>18</sup>. The final product represents the total amount of iron gained in the circulating blood during the period of hemoglobin rise. The percentage of iron utilization is then determined by dividing the total amount of iron gained in the circulating hemoglobin ( $\times 100$ ) by the amount of iron given orally.

Chart 8 records the percentage of utilization of iron in eighty-one cases. The percentage of utilization of small doses was, of course, much higher than that of large doses. Seven patients who received a total of less than 5 Gm. of metallic iron during the entire period of treatment

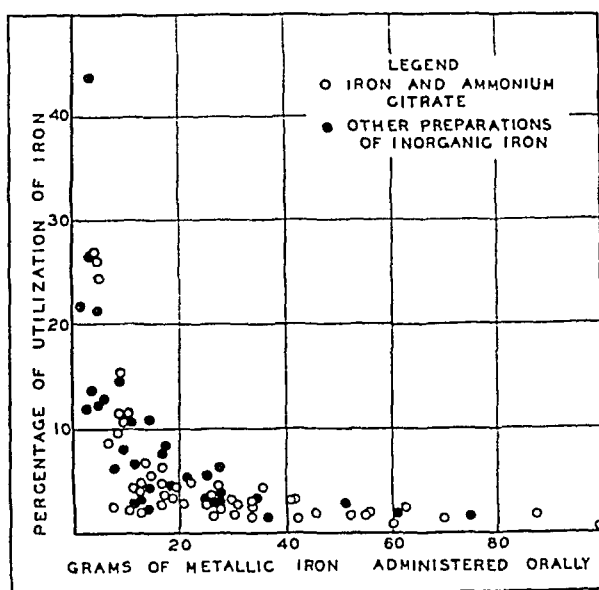


Chart 8—The percentage of utilization of iron in the formation of new circulating hemoglobin in eighty-one cases of hypochromic anemia during the entire period of hemoglobin rise. The percentage of utilization of iron from iron and ammonium citrate is shown to be similar to that of iron from other preparations.

attained a utilization of over 20 per cent. The few cases in which there were low dosage and low utilization were, for the most part, cases that were complicated by factors known to inhibit the formation of blood such as sepsis or a malignant process. The figure shows, also, that the percentage of utilization of iron from iron and ammonium citrate was similar to that from the other forms of iron given.

Additional data have shown that the percentage of utilization of iron early in the course of recovery from anemia tends to be considerably higher than the figures recorded in chart 8, which are for the total period

<sup>18</sup> Murphy, W. P., Lynch, R., and Howard, I. M. The Value of Determinations of the Iron Content of Whole Blood, *Arch. Int. Med.* 47:883 (June) 1931.

of recovery Three cases showed, early in the period of recovery, a percentage of utilization of about 50 That iron may be utilized to such a large extent is a fact that is not ordinarily appreciated The average utilization in all cases during the entire period of recovery was 34 per cent In contrast to this, the utilization in fifty-eight uncomplicated cases, during the first thirty days after iron therapy was commenced, was 11.8 per cent The average utilization of iron in the thirty-three cases of idiopathic hypochromic anemia during the total period of recovery was 31 per cent, and a further contrast is shown by the fact that in the forty-one cases of anemia without achlorhydria due to a chronic blood loss the utilization was 55 per cent It is to be expected that the percentage of utilization of iron in idiopathic hypochromic anemia should be less than that in anemia due to a chronic blood loss without achlorhydria, since the absence of free hydrochloric acid in the gastric contents probably is a factor in preventing adequate absorption of iron

The information obtained by the determination of the percentage of utilization of iron must not confuse the fact already illustrated by the arbitrary and comparative tests, that larger doses of iron are definitely more valuable than smaller doses That large doses of iron are utilized to a lesser degree than small doses simply means that the amount of hemoglobin rise, though large, is not proportionately as great as the size of the dose of iron

A comparison of the parenteral administration of iron with the oral administration of iron as regards the utilization in the building of hemoglobin is interesting, and is discussed in a separate communication<sup>19</sup> Factors of intestinal absorption do not enter into the problem of the utilization of iron administered parenterally In cases of hypochromic anemia in which the patients are given iron by the parenteral route, the percentage of utilization approaches 100, and therefore the amount of iron injected is closely related to the amount of iron gained in the circulating hemoglobin

#### THE MAINTENANCE DOSE OF IRON IN IDIOPATHIC HYPOCHROMIC ANEMIA

Patients with idiopathic hypochromic anemia, in contrast to those with hypochromic anemia due to a chronic blood loss or other causes, usually require either the continuous administration of iron or frequent courses of iron therapy in order to maintain a normal level of hemoglobin<sup>20</sup> There have been nineteen patients with this disease who have

19 Heath, C W, Strauss, M B, and Castle, W B Quantitative Aspects of Iron Deficiency in Hypochromic Anemia The Parenteral Administration of Iron, *J Clin Investigation* **11** 1293 (Nov) 1932

20 Heath, C W Idiopathic Hypochromic Anemia with Achlorhydria, *M Clin North America* **15** 1015, 1932 Witts<sup>2</sup>

been followed for over one year and who omitted iron following the initial recovery of their blood to normal. In all but five patients a definite drop in the hemoglobin occurred, which soon returned to normal when adequate iron medication was reinstituted. Of the five patients who maintained their hemoglobin level after iron was omitted, two showed a return of the acidity of the gastric contents to normal. One of these was a man who for years previous to treatment with iron had indulged excessively in alcohol but did not do so after treatment was commenced. In these two cases, an improvement in gastric function undoubtedly permitted a more normal absorption of hemoglobin-building substances of the food, and therefore rendered the renewal of iron medi-

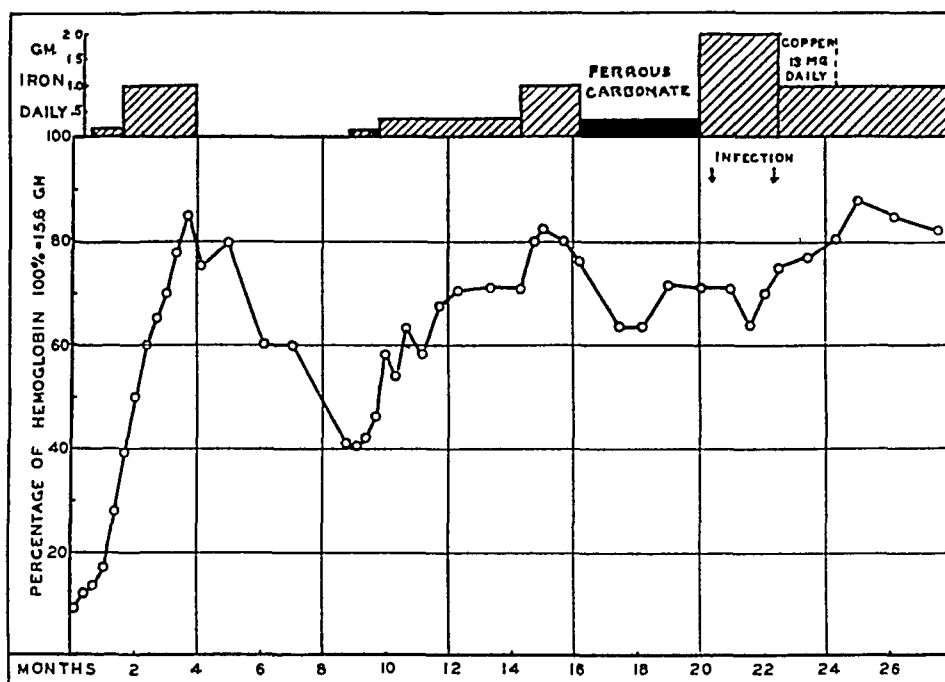


Chart 9—The changes in the hemoglobin percentage in a case of idiopathic hypochromic anemia observed over two years. Iron was administered in the form of iron and ammonium citrate except as indicated. Note (1) the prompt decrease of hemoglobin when iron was omitted, (2) the rise of hemoglobin over 80 per cent only when 1 Gm of iron daily in the form of iron and ammonium citrate was given and (3) the failure of 2 Gm of iron daily to increase the hemoglobin in the face of infection.

cation unnecessary. The remaining three patients, who to date have not required a renewal of iron medication, probably will eventually need it, if the complete achlorhydria persists.

Chart 9 represents a prolonged observation on a patient with idiopathic hypochromic anemia who has required iron to maintain the hemoglobin level. The hemoglobin fell gradually over the course of four months when iron was omitted. In addition the chart demon-

striates a number of interesting points regarding iron therapy. When iron therapy was renewed in this patient, 80 mg of iron as iron and ammonium citrate daily produced an unsatisfactory rise of hemoglobin (only 10 per cent in one month). Three hundred and seventy-five milligrams apparently produced a somewhat faster response of hemoglobin, but not as rapid as when the patient was first treated and received iron in the large dose of 1 Gm a day. The hemoglobin fell again when 350 mg of iron was given in the form of ferrous carbonate. Then the occurrence of an upper respiratory infection with fever lasting for nearly two months apparently prevented the hemoglobin from rising over about 70 per cent, in spite of a daily dose of 2 Gm of iron. Thirteen milligrams of metallic copper was then given in addition to iron, but it cannot be said that it accomplished more than if iron had been given alone. The hemoglobin rose from 80 to 90 per cent when iron was given without copper.

It is difficult to say what would be the correct minimum maintenance dose of iron for this patient. A daily dose of 375 mg of iron maintained the hemoglobin at 70 per cent, and it is likely from experience with other cases that if this dosage had been given from the time of the first recovery period it would have kept the patient in a good state of health. This is similar to the maintenance dose suggested by Witts, which he states is not more than one third of the minimum effective curative dose, or about from 0.3 to 0.5 Gm of iron in the form of ferric and ammonium citrate, or from 0.07 to 0.1 Gm in the form of ferrous carbonate. It is logical that a smaller dose of iron is needed for the replacement of the normal loss of iron by excretion than for the building up of large amounts of new hemoglobin and the body reserves. However, in one patient 0.12 Gm of iron daily in the form of ferrous carbonate was insufficient to maintain the hemoglobin at a level of 80 per cent. Iron as iron and ammonium citrate in a daily dose of 0.5 Gm was insufficient in another patient while she was suffering from a recurrent loss of blood, but when the loss of blood had ceased, a considerably smaller dose was apparently satisfactory.

There is no question but that patients with mild cases of idiopathic hypochromic anemia with achlorhydria will sustain their blood level while taking an adequate diet, but when an additional cause for anemia occurs, such as a chronic or an acute loss of blood, a considerable degree of anemia may be produced which would not occur in a normal person. This can be attributed to small reserves of hemoglobin-building substances in the patient with idiopathic hypochromic anemia, even at a time when the hemoglobin level is nearly normal. On the other hand certain patients with idiopathic hypochromic anemia, even while taking a proper diet and one rich in iron-containing foods and protein and not suffering from a chronic blood loss or other causes of anemia,

cannot maintain their hemoglobin level for more than several weeks without taking relatively large doses of iron daily (from 0.3 to 1 Gm of iron as iron and ammonium citrate)

The maintenance dose of iron thus seems to vary considerably in different patients and also in individual patients at different times. Much depends on the reserve of iron and possibly other hemoglobin-building substances in the body, on the extent of the gastro-intestinal defect and on the composition of the diet. It is therefore necessary in treating these patients to adjust the maintenance dose of iron to the needs of the given patient, frequent hemoglobin determinations being necessary. It is probable, if large doses of iron are persisted in for a long time after the hemoglobin reaches normal, that the iron stores in the body may be increased. This would allow the hemoglobin level to be maintained for a certain time without iron being administered by mouth. One or two courses of iron therapy a year, lasting several months each, designed to maintain the store of iron in the body, will then be sufficient in many cases to keep the hemoglobin at a normal level, but it seems wise to administer the drug with regularity.

#### TOXIC SYMPTOMS FOLLOWING THE ORAL ADMINISTRATION OF IRON AND AMMONIUM CITRATE

Certain disagreeable symptoms are not infrequently met with when iron is administered orally to patients. They have been observed especially when iron and ammonium citrate is given, and the present discussion is concerned with symptoms observed following the administration of this drug, which has been employed to a large extent in this study. Low abdominal cramps and diarrhea are the most common complaints, but these are apt to occur only during the first few days of iron therapy. If the iron medication is persisted in, the diarrhea and cramps usually disappear. Ambulatory patients are much more apt to experience these symptoms than patients who are in bed. Constipation may sometimes accompany the giving of large doses. General malaise, nausea and vomiting, symptoms that follow the parenteral administration of iron and ammonium citrate,<sup>19</sup> have been observed in a few instances. However, these symptoms have never appeared extremely severe or dangerous.

The extremely toxic properties of iron become evident practically only when it is administered parenterally in doses above 16 mg. Some of the toxic symptoms resulting from iron administered orally are due perhaps to an unusually rapid absorption of iron. Hurst<sup>21</sup> has described an unusual case of acute iron poisoning in a patient who was given a large amount of iron orally. It seems wise, therefore, as a

<sup>21</sup> Hurst, F. H. A Case of Iron Encephalopathy, *Guy's Hosp. Rep.* **81** 243, 1931.

routine, to commence treatment with a small daily dose of iron (2 Gm of iron and ammonium citrate), gradually increasing it in the course of a few days to the desired amount. Minor symptoms are to be disregarded, since these generally disappear in the course of time as the patient persists in the treatment.

The maximum amount of iron administered orally that is eventually tolerated by patients is, as a rule, very large. One gram of metallic iron, in the form of 6 Gm of iron and ammonium citrate daily, was taken with ease by the majority of patients. Only three of the sixty-three patients with hypochromic anemia who received iron and ammonium citrate in this dosage had untoward symptoms. In one patient the dose of 0.5 Gm of metallic iron could not be exceeded because of diarrhea and abdominal cramps. On the other hand, in one patient symptoms of intolerance did not develop until 2 Gm of metallic iron, as iron and ammonium citrate, was given daily, and even this large dose was well tolerated by several other patients.

#### THE VALUE OF COPPER THERAPY IN HYPOCHROMIC ANEMIA

Because of the effectiveness of copper in addition to iron on nutritional anemia in rats<sup>22</sup> and on nutritional anemia in children,<sup>17</sup> there has recently been considerable speculation regarding the possible value of copper in hypochromic anemia in adults. The experimental data at hand suggests that the addition of copper adds no beneficial effect to that of iron in adult hypochromic anemia. As described, a curve representing the average maximal hemoglobin response of eighty patients with hypochromic anemia who were treated with large doses of iron has been constructed. Above the level of 50 per cent of hemoglobin, the rate of hemoglobin increase, as shown by this curve, is faster than that shown by a similar curve constructed by Josephs<sup>17</sup> for anemia in children treated by iron alone. This faster rate of hemoglobin rise seems to correspond more closely to Josephs' figures for the rate of hemoglobin increase in children who received copper in addition to iron. Chart 9, as has been explained, illustrates in a case of idiopathic hypochromic anemia the failure of the addition of copper to iron in bringing about a more complete restoration of the hemoglobin to normal than iron alone. Several similar experiments have likewise shown no conclusive evidence that copper added to iron is of value. This is not in accord with the work of Mills<sup>23</sup> and of Adamson and Smith,<sup>24</sup> who

22 Hart, E. B., Steenbock, H., Waddell, J., and Elvehjem, C. A. Iron in Nutrition. VII. Copper as a Supplement to Iron for Hemoglobin Building in the Rat, *J. Biol. Chem.* **77**: 797, 1928. Myers, V. C., and Beard, H. H. Studies in the Nutritional Anemia of the Rat, *J. Biol. Chem.* **94**: 89, 1931.

23 Mills, E. S. Idiopathic Hypochromemia, *Am. J. M. Sc.* **182**: 554, 1931.

24 Adamson, J. D., and Smith, F. H. Chronic Chlorosis, *Canad. M. A. J.* **24**: 793, 1931.



believe that iron and copper are more effective in the treatment of idiopathic hypochromic anemia than iron alone

It is well known that small amounts of copper and other metals are present as impurities in pharmacopeial preparations of iron salts, and it has been thought that these impurities may have a share in the effectiveness of these preparations. However, a solution of iron and ammonium citrate, freed from the metals of the copper-arsenic group by hydrogen sulphide, produced an excellent response in one case of idiopathic hypochromic anemia.

It is felt that the influence that the addition of copper to iron may have in the treatment of hypochromic anemia in adults is at the most a minor one. Copper may perhaps hasten the recovery of patients with certain types of anemia. The same final results may be attained, however, by large doses of inorganic iron salts. This fact, together with the possible eventual toxic effect of copper, renders it inadvisable to give copper salts as a routine measure in cases of hypochromic anemia.

#### COMMENT

Evidence has been given showing that the optimal dose of iron administered orally to patients with hypochromic anemia varies considerably in different persons. Therefore, a single optimal dose for all patients cannot be defined. Frequent determinations of the hemoglobin are necessary in each individual case in order to determine whether or not the dose that is being given is adequate. The rule that the hemoglobin should rise at a faster rate than 1 per cent per day when the hemoglobin is below 70 per cent of normal may serve as a rough guide for judging the adequacy of a given quantity of iron.

If the hemoglobin response is much less than 1 per cent per day, doubt is cast on the adequacy of the iron dose, providing the anemia is of a kind that can be expected to respond well to iron, and providing no complications, such as sepsis or severe damage to organs, are present to inhibit the effectiveness of iron.

Sepsis, malignant processes, chronic nephritis, cirrhosis of the liver or other complications, which may themselves be etiologic in anemia, do not contraindicate the use of iron therapy. Hypochromic anemia due to a poor diet or a chronic loss of blood and responding to iron may accompany these conditions. For example, the anorexia accompanying typhoid fever or pulmonary tuberculosis may lead to the consumption of a diet low in many factors, including hemoglobin-building substances. The chronic loss of blood in cancer of the stomach or the hematemesis in cirrhosis of the liver may be the primary cause of hypochromic anemia in conditions responding to iron. The etiologic factors of the anemia in these conditions are usually difficult to judge, but may often be ascertained by an adequate trial with iron and by a complete study of the case.

To be certain of giving an adequate amount of iron in hypochromic anemia, it is necessary to give large doses, such as 6 Gm of iron and ammonium citrate, corresponding to 1 Gm of metallic iron daily. Economically, there is no objection to the administration of large amounts of inorganic iron, such as there is to the administration of large amounts of liver extract in the treatment of pernicious anemia, and as a rule large amounts of iron are well tolerated when given orally.

The problem of the oral administration of iron is one involving the quantitative correlation of the dosage with the influence on hematopoiesis. The clinical field for testing iron preparations may be quite well standardized by the careful selection of cases and the employment of adequate control periods. The effectiveness of iron preparations of unknown or doubtful value may then be compared to well known potent preparations. In this way accurate knowledge of the adequacy of treatment of human anemia with iron can be attained. Such knowledge will contribute to the better understanding and control of the etiologic factors in hypochromic anemia.

#### SUMMARY AND CONCLUSIONS

1 Eighty-four cases of hypochromic anemia have been analyzed with respect to the hematopoietic response to the oral administration of iron.

2 The factors necessary in the accurate clinical investigation of the effects of iron therapy are (1) the careful selection of suitable cases with regard to their type and etiology and the absence of complications and (2) the establishment of adequate control periods.

3 An arbitrary test has been described whereby the hematopoietic response to iron may be judged quantitatively, and the adequacy of the dosage of iron determined.

4 A comparative test has been described whereby several preparations of iron may be compared with one another as to potency.

5 Optimal dosage of iron in hypochromic anemia as judged by these tests, varies in different persons. Submaximal responses to large doses of iron are most often present in cases of idiopathic hypochromic anemia with achlorhydria and in cases complicated by sepsis, a malignant process or other conditions. Small doses of iron are, in general, less effective than large doses.

6 The percentage of utilization of orally administered iron as determined by the total amount of iron gained in the circulating hemoglobin, varies inversely with the size of the dosage. It is possible, during the period of rapid gain of hemoglobin when iron dosage orally is low, to have as much as 50 per cent of utilization. The average percentage of utilization of iron in the eighty-four cases during the

entire period of recovery was 3.4. The percentage utilization of iron in idiopathic hypochromic anemia is less than in uncomplicated hypochromic anemia due to a chronic loss of blood.

7 Patients with idiopathic hypochromic anemia usually require a continuation of iron therapy indefinitely. The maintenance dose of iron in these cases is usually smaller than the dose required for maximum blood regeneration in the period of recovery, but varies with individual cases.

8 Toxic symptoms following the oral administration of iron and ammonium citrate not infrequently occur, but the maximum amount of iron administered orally in this form that is eventually tolerated by the patients is, as a rule, large (from 1 to 2 Gm. daily).

9 It is felt that the influence that the addition of copper to iron may have in the treatment of hypochromic anemia in adults is at the most a minor one, and that it is inadvisable to give copper salts as a routine measure in hypochromic anemia in adults.

10 To be certain of giving adequate amounts of iron in hypochromic anemia, it is necessary to give large doses, such as 6 Gm. of iron and ammonium citrate daily, corresponding to 1 Gm. of metallic iron. Ferrous salts can be equally effective in somewhat smaller doses.

## Book Reviews

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**Pituitary Body, Hypothalamus, and Parasympathetic Nervous System**  
By Harvey Cushing, Professor of Surgery (Emeritus), Harvard University,  
and recently Surgeon-in-Chief Peter Bent Brigham Hospital, Boston Price, \$5  
Pp 234, illustrated, indexed Springfield, Ill Charles C Thomas, 1932

This latest book of Dr Cushing's has been available before in sections, for it comprises the papers that were the foundation for four lectures on related subjects. The Lister Memorial Lecture given before the Royal College of Surgeons of England on July 9, 1930, the William Henry Welch Lecture given at Mount Sinai Hospital, New York, on April 30, 1931, the Alpha Omega Alpha Lecture given at Yale University, on Feb 24, 1932, and the Balfour Lecture given at the University of Toronto on Lister Day, April 8, 1931. Each paper presents an aspect, clinical or experimental, bearing on the function and interdependence of the pituitary body, hypothalamus and parasympathetic nervous system, and provides in itself ample fact for new clinical concept and for imaginative rumination.

Left separate, the papers may lose some force because only one facet of the question is touched on in each of them. Brought together, however, as has been done in this book, they add to each other, to round out a complete picture which stimulates the imagination in a way that is quite overwhelming. The book reads as easily as a novel, despite its colossal erudition, and presents a fascinating opportunity to those who enjoy following the reflections of a first-class and vastly experienced intelligence on a romantic and little understood subject.

The first paper, "Neurohypophyseal Mechanisms from a Clinical Standpoint," surveys the evidence concerning the functions of the anterior hypophysis, infundibulum, posterior hypophysis and hypothalamus, and their dependence on each other. Clinical examples are described in which there have been lesions of one or the other of these structures, and the resultant symptoms, or lack of them are correlated with the physiologic facts from which various current hypotheses have been evolved.

The second paper, "Posterior Pituitary Hormone and Parasympathetic Apparatus," is a remarkable experimental study of the effect of the introduction of different substances into the cerebral ventricle. It is divided into eight parts, the first of which describes the reaction of human subjects to intraventricular pituitary extract. The others go on to describe similarly the effects of intraventricular pilocarpine, histamine, atropine and tribromethanol, to show the counteractive effects of some of these substances, and to contrast their intraventricular effects with those produced when they are injected elsewhere in the body. To describe and discuss the many astonishing phenomena which were produced is not the function of this review. Suffice it to say that enough hitherto undiscovered information is accumulated about the action of these drugs when placed directly in the neighborhood of the neurohypophyseal mechanism to stimulate a great advance in knowledge of it, as well as to suggest new routes for investigative method.

The third paper is one that attracted attention everywhere, since it described for the first time, in a style unsurpassed for its clarity and vision, a new and heretofore unrecognized clinical syndrome, "Pituitary Basophilism." So keen was the discernment in ferreting out this rare and unusual pituitary aberration, and so accurate was the differentiation of its symptoms, that the underlying pathologic process, basophil adenoma of the hypophysis, was actually correctly predicted in cases which had previously been reported by other authors as showing polyglandular dystrophies of unknown origin.

The fourth paper, "Peptic Ulcer and the Interbrain," is perhaps more speculative than the others, and yet Dr Cushing is always careful not to go from fact to fancy without forewarning the reader, and without giving him the groundwork

and leaving him the leeway to form his own conclusions. A number of cases are cited in which there has been disturbance in the neurohypophyseal mechanism, and in which peptic ulcer, acute or chronic, has been an associated finding. To these cases are added certain experimental facts tending to shed more light on the neurogenic theory of ulcer formation. That the incidence of peptic ulcer as a complicating factor in intracranial pathology is high is incontrovertible.

It is always a temptation for a reviewer to make his review a synopsis. While that could have been done in this instance, it was felt that to provide a mere recital of salient facts would have led some readers of these paragraphs to feel that the essentials could be absorbed from it without digesting the original. That is less true of this book than of any other of similar scope in this reviewer's ken. The manner in which the subject matter is presented, the fields that are opened to the reader's imagination and the way in which his knowledge is not only brought to date, but carried into the future make it imperative that the work itself be read. And more is the wonder when one considers that it is the work of a man who has always carried more than his share of active clinical burden sufficiently well as to be assured of a place in posterity as one of the great surgeons of all time.

**Diseases of the Thyroid Gland** By Cecil A. Joll. Price, \$20. Pp. 682.  
St. Louis: C. V. Mosby Company, 1932.

This book is presented as "an account of thyroid diseases in sufficient detail to be of value to senior students and practitioners of medicine, and even possibly to consultants who may be without special opportunities for the frequent observation of goitrous patients."

The opening chapters of the book, in which the structure, development and physiology of the thyroid gland are reviewed, are of especial interest and value in view of the recent advances in knowledge of these subjects. One chapter is devoted to the structure and physiology of the parathyroid glands. This is followed by several chapters dealing with detailed clinical, pathologic and physiologic considerations of inflammatory and parasitic diseases of the thyroid gland, lymphadenoid goiter, developmental abnormalities, simple goiter, the hypothyroid states, neoplasms, thyrotoxicosis and the cardiovascular system in thyrotoxicosis. One chapter is devoted to a consideration of medical treatment and of treatment by irradiation for primary thyrotoxicosis. Surgical treatment of primary thyrotoxicosis is described in detail, and anesthesia, surgical technic in various types of cases and postoperative complications are all carefully considered and described.

Throughout the book illustrations are used profusely. There are many excellent colored plates. The illustrations are a distinct aid to avoidance of confusion in terminology. Carefully prepared lists of synonyms also help to avoid such confusion.

So many considerations of thyroid disease are hypothetical that it would seem impossible for any book on the subject to meet with the complete agreement of all readers. The author has given the principal opinions deserving of consideration on most of the controversial aspects of thyroid disease, and has also expressed his personal opinion in each case. Not all of the opinions so expressed coincide with the views most widely held in this country. This does not detract in the least from the value of the work, however, because ample consideration is given to the opposing views, and because the established fundamental principles of diagnosis and treatment are supported throughout the book.

The technic of surgical operations in various types of goiter is described in meticulous detail, and the recognition and treatment of postoperative complications are thoroughly considered.

The bibliography is most complete and is arranged at the ends of the chapters, thus greatly enhancing its value to those more than casually interested in the subject.

The book, beside being useful to the groups indicated in the author's preface, should prove of value to students of diseases of the thyroid gland and as a reference work

**Streptococci in Relation to Man in Health and Disease** By Anna W Williams Price, \$5 Pp 260 Baltimore Williams & Wilkins Company, 1932

The attempt to simplify for the student the vast complexity of modern medicine by the monographic method receives a notable addition in Dr Williams' book on streptococci. For years a thorough student of bacteriologic problems and always on the firing line in the battle against disease, she assembles here a great storehouse of knowledge on all matters pertaining to this ubiquitous and treacherous group of micro-organisms. In matters dealing primarily with the biologic aspects of the problem, Dr Williams writes with authority and confidence, her personal interpretations are both stimulating and convincing. But the sections dealing with clinical relations—applied bacteriology, if you will—lack, perhaps, a little of the spontaneity of the earlier chapters. The author has achieved the purpose, to be sure, of assembling all the important information, but here there is more the atmosphere of a compendium. The important questions (to the clinician) of focal infection and elective localization, for example, are dealt with in a slightly vacillating manner, and after the extensive summary of "streptococcic claims" in the etiology of rheumatic fever, one is disappointed that Dr Williams is silent as to what she herself really thinks there is of sense, if any, in all this tangle. The summary (page 193) to the effect that "there is evidence to substantiate the hypotheses that hypersensitiveness or hyperergy to various strains of streptococci among alpha, gamma and beta types is the cause of an acute clinical rheumatic fever attack in those who by reason of several other factors also are ready for such an attack" is a *reductio ad absurdum*, which is hardly fair to the reader, when one might have said, "we really do not know at present just what the relation of streptococci to rheumatism is." One is also surprised to find that the role of streptococci in the common disease tonsillitis receives only casual mention, when a whole chapter is given to septic sore throat, a relatively insignificant subject. Even more disappointing is the lack of analysis of the relation of streptococci to Bright's disease—certainly a matter for lively discussion—which is dismissed with the bare statement (page 76) that "in the genito-urinary tract streptococcus infection may occur such as cervicitis, orchitis, urethritis, cystitis and nephritis."

A few odd errors in the text, doubtless to be corrected in a subsequent edition, escaped the proofreader, such as "wholeproof" for "hole-proof" and "hyperurgy" for "hyperergy."

**The Sex Technique in Marriage** By Isabel M Hutton, M D Price, \$2 Pp 160 New York Emerson Books, Inc, 1932

This is the first American edition of a book which so far has appeared in three English editions and one Dutch. It made its first appearance in 1923, and was published by Heinemann.

The American edition is essentially the same as the ones previously published in England, and these already have been reviewed competently. *The Journal of the American Medical Association* (82 153 [Jan 12] 1924) has described the first English edition as a practical work on the subject it discusses, written in plain, understandable language, and with good judgment as to what constitutes general medical opinion. This is a fair characterization of the current American edition. One might raise the question as to the necessity for a book of this character and agree with the *Medical Journal of Australia* that there is a limited sphere of usefulness for it, or one might reflect with the *British Medical Journal* as to how curious it is that civilization in man should have led to a necessity for instruction in such a natural instinctive act as consummation of marriage.

The book appears to suffer from an inferiority complex, which is unfortunate. It is too obviously self-conscious, and is published in this country by a firm hitherto unknown to libraries and booksellers, on the last few pages are reprinted many of the nice things that have been said of the earlier English editions by complimentary reviewers. This sort of self-advertising is likely to seem in bad taste to certain readers and is entirely unnecessary. Almost any one will admit that whatever demand there may be for a book containing this sort of instruction is well and honestly met by this volume. As President Lincoln is supposed to have said of a certain book, any one who likes this kind of book will find it just the kind of book they like.

**Differential Diagnosis of Endocrine Disorders** By Allan W. Rowe, Director of Research, Evans Memorial, Massachusetts Memorial Hospital, Boston. Price, \$4. Pp 220, with 50 tables. Baltimore: Williams & Wilkins Company, 1932.

The material for this monograph was drawn from investigations in endocrinology which have been carried on at the Evans Memorial Laboratory since 1912, and summarizes observations made on a large group of people. The book is divided into three parts, these deal with a clinical consideration of the persons studied, with laboratory tests and with certain special examinations that have been completed.

Great emphasis is laid on the results of chemical tests as indicators of glandular function. The diagnosis of hypofunction, hyperactivity or dysfunction of any of the endocrine glands was accepted, however, only after exclusion of all known "non-endocrine" causes of variation from normal in the tests utilized. Some of the tests are not of much value to the internist, since their results may be affected so markedly by metabolic trends which are independent of internal secretions.

The tables include data yielding suggestive information in regard to the possible correlation of many different physical and chemical findings. To assemble these data, normal persons were compared with patients studied in a similar fashion but having endocrine disorders. A particularly valuable and interesting feature of the volume lies in the careful account it contains of the methods by which a complicated program of diagnostic studies can be completed without undue expenditure of time. These schedules should prove useful to clinics engaged in carrying on intensive research in endocrinology.

**A Guide to Human Parasitology for Medical Students and Practitioners** By D. B. Blacklock and T. Southwell. Price, \$4. Pp 271. Baltimore: Williams & Wilkins Company, 1932.

The reviewer's first reaction to this guide to parasitology was "Well, why has this inevitable performance not been done before, why has relief not been brought sooner to the long-suffering general practitioner?" For this, in his opinion, is precisely what Blacklock and Southwell have done for those of us who, only occasionally seeing an instance of infestation with those fascinating "animals," have either regarded the subject as a terra incognita or at best have had a confused vision of crawling and creeping things attacking man, pig, cow, snail, fish and insect—a sort of a grand nature-fakery. Nor is the situation much relieved by turning to technical works on parasitology, for there one runs foul at the start of dentigerous ridges, gubernacula, cervical papillae and bursae copulatrices, not to mention plerocercoids and hexacanth embryos. In the present book all these difficulties are swept away and everything is made clear in a delightfully simple and yet thoroughly scholarly way, the matter becomes not only readable but almost romantic. Especially valuable aids to the nontechnical student are the admirably documented illustrations and charts and the tables in which the subject matter is classified from every possible point of view. Every medical student should have this compendium on his shelves.

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## "DYSPITUITARISM" TWENTY YEARS LATER

WITH SPECIAL CONSIDERATION OF THE PITUITARY ADENOMAS

HARVEY CUSHING, M D

BOSTON

While so much that is new and important is being accomplished by younger men, it is a great compliment to be asked a second time to deliver one of these lectures, and in venturing to address you again on the same topic as before, I can only plead that in spite of unavoidable and often protracted interruptions, it has continued to engage much of my time and thought. Were every lecturer made to understand that after the lapse of twenty years he would be requested by the Society to give an accounting of his original thesis to see what, if anything, it had amounted to in the interim, such a program would, to say the least, foster conservatism of statement at his inaugural appearance.

At a meeting of the Society on December 10, 1910, under the title "Dyspituitarism," the attempt was made to throw some light on an obscure subject—the disorders of pituitary function—then of interest to few. Of that address, which I have forced myself to reread, the less said the better. It was soon amplified into a book, long since washed away in the ever increasing flood of hypophysial literature, now pouring over the dam, and to which all departments of medicine in clinic and laboratory are adding their quota.

I scarcely recall what first led us, soon after the opening of the Hunterian Laboratory in Baltimore in 1905, to attack such an unpromising problem.\* It had its surgical aspects, to be sure, in that all pituitary

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The Harvey Society Lecture, as given in part, Jan 19, 1933, at the New York Academy of Medicine

\* Alfred Frohlich and I had been co-workers in Sherrington's laboratory in Liverpool in 1900, in which year, unknown to us, Babinski<sup>10</sup> had reported, under the title, "Tumor of the Pituitary Body Without Acromegaly," the case of a girl of 17, showing, at autopsy, arrested development of the organs of generation. In the following year, Frohlich reported,<sup>56</sup> under an almost identical title, an example of the same syndrome in a boy of 16, the nature of the lesion not having been verified. In December, 1902, there died in Dr. Osler's wards at the Johns Hopkins Hospital a sexually undeveloped girl of 16 with the symptoms described by Babinski, and whose case was subsequently reported in my first paper which in any way pertained to the pituitary body.<sup>33</sup> While Babinski unquestionably is entitled to full priority in regard to this syndrome, it was popularized in Vienna through the interest aroused by the discussion of Frohlich's paper.



disorders then known were somehow associated with tumors, but they were supposedly uncommon and because of their situation hopelessly unapproachable

Just what might be the syndrome—if there was such a thing—of lost or impaired pituitary function was unknown. Indeed, there was no certain proof that Marie's acromegaly was not an expression of glandular deficiency. To be sure, certain states, called "adipositas cerebialis" (Schuster) and "adiposogenital dystrophy" (Bartels) had been the subject of discussion. But it seemed highly questionable whether these peculiar adiposal syndromes, which were sometimes associated with diabetes insipidus, had anything to do with the pituitary body, and whether they had any relation to acromegaly, in which malady gross hypophysial tumefactions might or might not be found after death, was still more doubtful.

Many were inclined to ascribe pituitary disorders to some perversion of secretion rather than to a quantitative loss or increase of the normal secretory product, whatever that might be—if indeed there actually was any such product in the anterior lobe. Though the belief had already been expressed by Benda<sup>16</sup> (1900) that hyperplasia of acidophilic elements, apparently in a stage of secretory activity and therefore representing an adenoma, was a distinctive feature of acromegaly, others (e.g., Dean Lewis<sup>81</sup>) described an acidophilia apparently without adenomatous delimitation. However, at the time of which I speak, pathologists took little interest in the adenopathies as such, and most of the soft cellular unaccountable enlargements of the gland were regarded as sarcomas, or the noncommittal term "struma pituitaria" was applied to them.

With our knowledge of the pituitary disorders in this chaotic state it was learned in the course of a series of operations on the canine hypophysis that enucleation of the posterior lobe (surprisingly enough in view of its proved pharmacodynamic properties) caused no appreciable effect, whereas in adult animals a peculiar form of fatal cachexia supervened when the entire gland was removed. The fatal issue we thought could be postponed by glandular implantations or by injection of emulsions,<sup>31</sup> but what was of greater significance, it was finally observed that those animals which had recovered after subtotal extirpations of the gland tended to become obese and sexually dystrophic—an experimental state comparable to adiposogenital dystrophy<sup>34</sup>

And when shortly after this it was reported, first by Bernhard Aschner<sup>7</sup> (1910), that immature puppies not only tolerated hypophysectomy better than adult animals but remained dwarfed and sexually infantile, it was obvious that the syndrome of Frohlich was truly a

deprivation disorder, suitably called *hypopituitarism*. This having been established, it was highly probable, all things considered, that acromegaly must represent the counter state of *hyperpituitarism*, indeed, one or two partly successful operations for acromegaly had led to an apparent amelioration of symptoms shown by a shrinkage of the hypertrophic hands and feet.

At the same time, it was clinically apparent that all examples of pituitary disease did not unmistakably fall in these two categories, certain adipose and sexually dystrophic adult patients with undifferentiated pituitary "strumas" might show traces of antecedent, or what has since been described as "fugitive" acromegaly,<sup>11</sup> while others in whom acromegalic changes had become pronounced tended in time to become fat and amenorrheic or impotent. These mixed syndromes consequently were taken to represent intermediary or overlapping states of disordered function conveniently classified as examples of *dyspituitarism*—whence the title of my former lecture.

While this conception of the pituitary disorders appeared at the time to be a satisfactory working basis, its weak points soon became apparent. Erdheim<sup>48</sup> had already (1904) shown that the usual tumor causing the syndrome of Frohlich was of congenital origin, and suprasellar in situation, and since it was prone to deform the interbrain, he was led to attribute the syndrome largely to a diencephalic rather than a glandular source. On this basis, the acute cachexia as well as the more chronic adiposity and sexual dystrophy my co-workers and I had described<sup>32</sup> might conceivably have been due to unavoidable hypothalamic contusions produced by Paulesco's intracranial method of approaching the gland, which we had adopted.

While it was not then known that the functional interdependence of hypophysis and hypothalamus is such that they can scarcely be discussed separately,<sup>37</sup> nevertheless, from these early canine experiments there were glimmerings, solely from a hypopituitary or deprivation aspect, to be sure, of an important influence exercised by the anterior lobe on the factors of growth and of sex. At the same time, striking secondary changes, particularly in the thyroid gland, had been observed, together with a greatly increased tolerance for carbohydrates, which needed explanation.<sup>60 134</sup>

It is incredible that from so small and unpromising an acorn there should have sprouted—or appear to have sprouted—in so short a time as twenty years such a far reaching and diversified plantation of interests. The literature of the subject in its many ramifications has become so enormous no one can pretend to keep pace with it, far less to comprehend it all in view of the contradictions and subtleties—not to say speculations—with which it has become enmeshed.

Attention has periodically switched from a consideration of the gland as a whole, to the posterior lobe, to the anterior lobe, and back again to a study of the separate properties of extracts of anterior or posterior lobe or of the tuberal cuff, and to the effect on them of hypothalamic stimulation or paralysis

Some few have worked upstream to explore the central neuroglandular mechanisms that are involved, but a far greater number have worked downstream to examine the isolated effects of extracts on remote tissues and subsidiary organs. A fly could scarcely be cast anywhere in these waters, even by a novice at research, without hooking something deserving of experimental study, and for this purpose a goodly percentage of the animals in the ark, the amphibians below it and the doves about it have successively been utilized

Out of all the present welter of discovery relating to the internal secretions, it becomes increasingly evident that the pituitary gland holds a dominating position in the endocrine series and exercises direct or indirect control over an unsuspected number of biochemical processes of utmost importance to the economy of the body. And should one venture to single out, from many, those particular steps that in recent years did most to accelerate our progress, they were the discovery in the anterior lobe of the two separable hormones of growth and sex. For these steps the brilliant experimental studies of Herbert M. Evans, on the one hand, and of Philip E. Smith, on the other, each with his several collaborators, were largely responsible

But it is one thing to make discoveries through animal experimentation and quite another to correlate them with disease, and there is great need of an integrator to lead by the hand, through the present maze of scientific investigation, those who must deal with the victims of disordered pituitary function at the bedside. Were all human beings, male and female, as much alike as are standard rats of either sex, the clinician's difficulties might be ameliorated. Yet even rats of the purest strain show marked individual variation and fail to react precisely alike when injected with a pituitary hormone, whereas Nature's experiment of a similar kind on isolated examples of our own highly mongrel species may give results so bizarre they as yet exceed all power of interpretation

To some of the etiologically obscure maladies that already have come to be laid at the door of pituitary dysfunction I shall have occasion to allude, and we may confidently expect that many more hitherto unexplained pathologic states will prove in time to be related to the neuro-biochemical imbalance of this amazing gland. But the field is now so large it would be futile in a single address to cover more than a small corner of it, and, summing that a consideration of the adenomas and

their effects would at this time be as likely as any other to be of general interest, I shall confine myself to this single topic

*Pituitary Adenomas*—For an understanding of these tumors we must necessarily begin with the cellular composition of that portion of the gland which Beiblinger chooses to call the adenohypophysis<sup>\*</sup> to distinguish it from the neurohypophysis. While much unquestionably remains to be learned of the life history of the adenohypophysial cells (by perfected stains or by methods of intravital study or artificial cultivation as yet undeveloped), in the normal adult gland only three cellular elements, as originally described by Schonemann (1892), continue to be distinguished by histologists. More properly speaking, however, they represent a single or chief element in two differing stages of activity

This chief element, the primary mother-cell, possesses a finely granular, nonstaining (chromophobe) cytoplasm, which in the process of ripening acquires coarse secretory granules of two distinguishable types known as acidophilic and basophilic<sup>†</sup> from their peculiar reactions to dyes. What is more, these ripened cells, as Severinghaus has recently shown,<sup>112</sup> not only have their individually characteristic paranuclear Golgi apparatus (that of the basophilic elements being distinguished by a ring, that of the acidophils by a filamentous net), but the predetermination of the change into basophilic or acidophilic elements is actually indicated (cf fig 1) by the morphology of the Golgi body in the mother-cell—an important disclosure to which I shall return (cf p 496)

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\* This convenient term, occasionally used herein, permits one to escape from the awkward employment of "anterior-pituitary" as an adjective which even abbreviated to A. P. has come into common use. To the uninitiated, much of the recent German literature has become unreadable from the employment of such codes. In his recent comprehensive monograph,<sup>21</sup> Beiblinger particularly emphasizes the functional unity of the adenohypophysis, the anatomic subdivisions of which (*pars anterior, intermedia et tuberalis*) he believes to be indistinguishable in man. But while this may be anatomically correct, it is physiologically embarrassing since there is every reason to believe that the neurohypophysis is activated by the enveloping portion of the adenohypophysis, and they can scarcely, therefore, be separately discussed.

† A fourth and a fifth element (the "pregnancy cells" of Erdheim and Stumme and the "castration cells" of Zacherl) are recognized, and numbers of highly similar cells are present in the gland in states of thyroid insufficiency. They all appear to be merely enlarged mother-cells which are arrested in the process of ripening through the exigencies of the physiologic state that produces them. Whether they are forerunners of acidophilic or of basophilic elements is disputed, and this may vary in different species. The nature of the Golgi bodies in the different types would probably decide the question.

The chromophobe mother-cells normally outnumber the others\* and, as the character of their cytoplasm would indicate, appear to give off no secretory product, whereas the acidophilic and the basophilic elements unquestionably are in the process of elaborating, each its own peculiar active principle. We furthermore have fairly conclusive evidence that the separable growth-promoting principle is derived from the acidophilic elements, and there is some indirect evidence which suggests that the sex-maturing principle may be associated with the basophilic elements.

So far, this would seem simple enough—three distinguishable cell types—two of them actively secreting—a hormone accredited to each

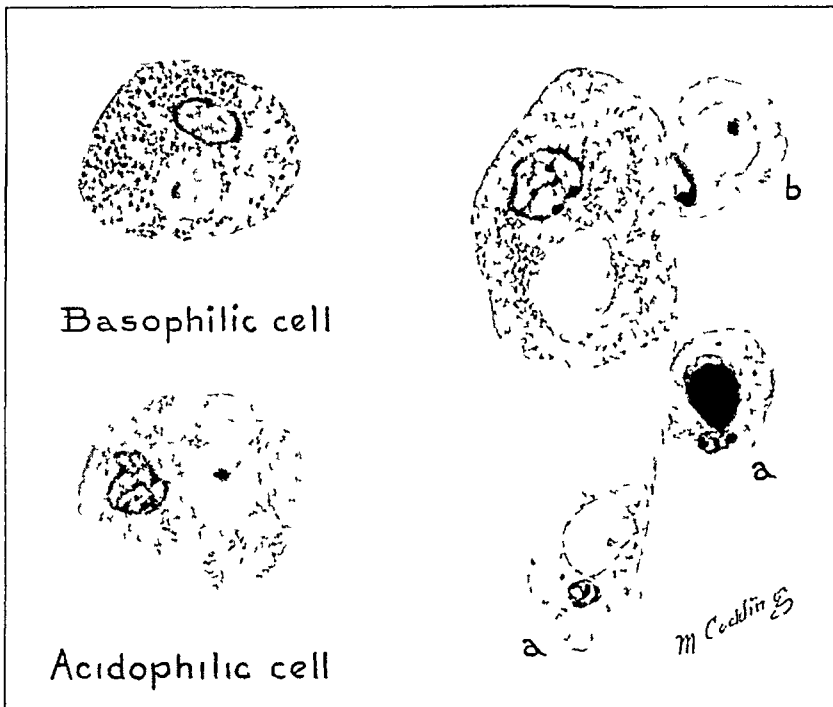


Fig 1—Drawing from hypophysis of monkey to show (left) acidophilic “net” and basophilic “ring” types of Golgi, and (right) large acidophilic cell with three chromophobe elements (b) basophilic, (a) acidophilic

But we unhappily are not permitted rest at this point, for highly competent observers are convinced that the anterior pituitary gives off several other separately identifiable hormones. This must mean either that there are more types of secreting cells in the gland than heretofore believed, or else that the ripened product of the two known types has a variable action under different circumstances. It is conceivable that

\* Rasmussen<sup>104</sup> finds in the “normal” gland 52 per cent chromophobe, 37 per cent acidophilic and only 11 per cent basophilic cells

the secretory product of a given cell may not always have precisely the same chemical formula, or even that a cell may discharge a cytoplasm of variable quality in different stages of ripening. But neither of these possibilities seems at all probable, and some other explanation may be forthcoming.

Now what, from a clinicopathologic standpoint, is highly significant in connection with this is the fact that only three types of pituitary adenomas are recognized. One is composed of chromophobe elements apparently identical with the nonsecreting mother-cells, in another, acidophilic elements abound, its clinical manifestations being those of overgrowth, while the third is purely basophilic in composition, its astonishing effects being conceivably ascribable to an excess of the gonad-stimulating principle. It is possible, of course, that those who have chiefly studied these pituitary adenomas have been influenced by preconceived ideas of what they should find, and there may be more types than have as yet been identified, but this appears unlikely. We, therefore, have neither cell type nor corresponding adenoma formations to represent more than three possible hormones, and the purely chromophobe adenomas, for reasons to follow, we may discard as having no secretory activity.

Adenomas of the ductless glands have long been known. To some of them processes of disease have been ascribed, but aside from the attribution of the acidophilic adenomas of the pituitary body to acromegaly and of the so-called fetal adenomas of the adenoma to hyperthyroidism, they in the past have usually been regarded by pathologists as functionally inert conglomerations of cells of no particular consequence. But a revolution in this idea has come about through the recent disclosure that a tiny adenoma of a parathyroid glandule of pancreatic islet tissue, or of the basophilic elements of the pituitary body, represents clusters of cells in an otherwise normal organ possessing a secretory potency and activity of astonishing degree.

In fact, the experimental reproduction of a hypersecretory syndrome by the successive daily injections of a glandular extract is a feeble imitation of the uninterrupted outpouring of an excess of the natural hormone from one of these hidden pathologic "stills." No moonshiner, with every effort to throw searchers off the track, ever secreted the spot where his demoralizing product was being distilled and prepared for distribution more skilfully than Nature has done in the case, for example, of that remarkable disease, deforming osteitis fibrosa, whose gross skeletal changes von Recklinghausen fully described over forty years ago in complete ignorance of their fountain-head.

# 1 THE CHROMOPHOBE ADENOMAS AND THEIR SYSTEMIC EFFECTS

To most of the known adenomas of the ductless glands, like those of the thyroid, parathyroids, pancreatic islets and adrenal cortex, a hypersecretory function is now ascribed. And this, as we shall see, is true also of the acidophilic and basophilic adenomas of the anterior pituitary, whereas the more common chromophobe adenomas, to which we may first turn, appear to be an exception to the rule.

Several histologic types of chromophobe adenomas have been described,<sup>11-12</sup> differing somewhat in their architecture and life history. All of them, however, are composed of cells having a nonstainable cytoplasm resembling the mother-cells and not until

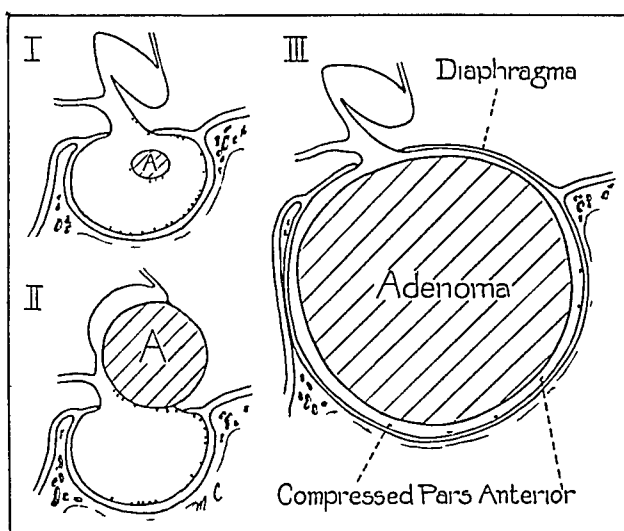


Fig 2—Diagrams of chromophobe adenomas (A) to show I, small, nonsymptomatic lesion, II, a suprasellar lesion with chiasmal involvement but no secretory effect, III, an intrasellar lesion sparing chiasm but with dual hypopituitary effects from compression of glandular elements

they reach a size sufficient to expand the membranous and bony envelope of the gland do they produce any recognizable constitutional disorder.<sup>65</sup> By this time the degree of intrasellar pressure has often become such that the residual of the normal gland is peripherally so thinned out the merest traces of it can be identified on histologic sections (cf fig 2 III). The symptomatic consequences of such a slow inactivation by compression are purely hypopituitary,

and the resultant adiposogenital dystrophy differs in no respect except in its more insidious onset, from that which follows a subtotal hypophysectomy in the dog or rat, dwarfism being added to the picture if a preadolescent subject is the victim either of the disease or of the experiment.

Operations for these chromophobe adenomas are undertaken largely to preserve vision, for the expanding lesion stretches and distorts the overlying optic chiasm. And while this has no bearing on the present topic, what does pertain to it is the fact that after one of these soft expanding tumors has been radically excavated, the compressed normal elements of the gland may, in fortunate instances, resume their functional activity. This is shown, for example, by the occasional resump-

tion of normal menstruation in women previously amenorrheic, for which there can be no other ready explanation than the release of the sex-activating cells from their pressure inhibition \*

Fragments of a chromophobe adenoma, so far as I know, have been tested only twice by implantation methods to determine the presence or absence of an active hormone, with contradictory results † There, however, is a further reason for believing that their clinical syndrome is not attributable to a secretory product This is based on the complete absence of any recognizable symptoms except those of chiasmal involvement <sup>36</sup> when one of these tumors, owing to a defective diaphragma sellae, has escaped from its intrasellar confinement and come to lie in such a position that the activity of the rest of the gland continues unimpaired (cf fig 2 II)

While this argument may appear to have been unduly belabored, it seems necessary at the outset clearly to distinguish between the two actively secreting types of adenoma, subsequently to be considered, and these chromophobe tumors whose somatic effects, so far as one can determine, are purely hypopituitary

Though the chromophobe adenomas are by far the most common type—the proportion in our series of 385 verified cases being 277 chromophobe, 107 acidophilic and "mixed," and 1 basophilic—the opportunity to study an early example post mortem has never arisen, and their more common point of origin is unknown They vary considerably in their histologic appearance, some of them having an architecture suggesting an origin from the pars intermedia, others being structureless masses of cells in whose cytoplasm nonstainable granules suggesting secretory activity may sometimes be detected

Whereas in the normal pituitary gland mitotic figures are not seen and are rarely if ever picked up in fixed and stained preparations of the adenomas, they occasionally may be detected on supravital preparations (cf fig 6) Nevertheless, these pituitary adenomas, while they may crowd their way into the cranial chamber and cause death, never seem to acquire malignant tendencies

A few examples, possibly 2 per cent of the 385 cases, have been called adenocarcinoma by pathologists who have examined the tissues But the fact that the patients from whom the specimens were taken, in spite of an incomplete removal of the lesion, have all survived the operation for many years belies the diagnosis of malignancy, and at the same time speaks in favor of their being composed of elements possessing no functional activity

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\* That the adiposogenital symptoms brought about by these adenomas are not ascribable to involvement of the interbrain by the enlarging tumor is evident from the fact that an associated tuberal polyuria is exceedingly uncommon and is rarely elicited by the surgical manipulations necessary to expose and remove one of them On the other hand, polyuria is a common feature of hypophysial duct tumors (craniopharyngiomas), the study of which led Erdheim to advance his hypothalamic explanation of the symptoms in Frohlich's disease And even should polyuria not have occurred spontaneously from the effects of a growth of this kind which is more apt to be suprasellar than intrasellar in position, it is almost certain to be produced by the operative manipulations necessary for its removal

† Kraus alludes briefly <sup>79</sup> to his having observed on a single test a positive follicular effect Berblinger,<sup>22</sup> on the contrary, observed no effect on a single test



Specimens removed at operation from a few of the tumors in our recent series have been studied by Dr Severinghaus who finds (1) that in the adenoma of acromegaly the Golgi body of all cells (fig 3), whether chromophobe or acidophilic, is of acidophilic type, (2) that in the chromophobe adenomas the cells with a Golgi body of acidophilic type far outnumber those with a Golgi body of basophilic type. While no opportunity has arisen similarly to investigate a pure basophilic adenoma, it can readily be seen that these cytologic clues demand close pursuit.

Further studies in this direction may throw light on the composition of what Bailey and I have called <sup>11</sup> "mixed" (chromophobe and acidophilic, never chromophobe and basophilic) adenomas, and may enable us to determine the nature of

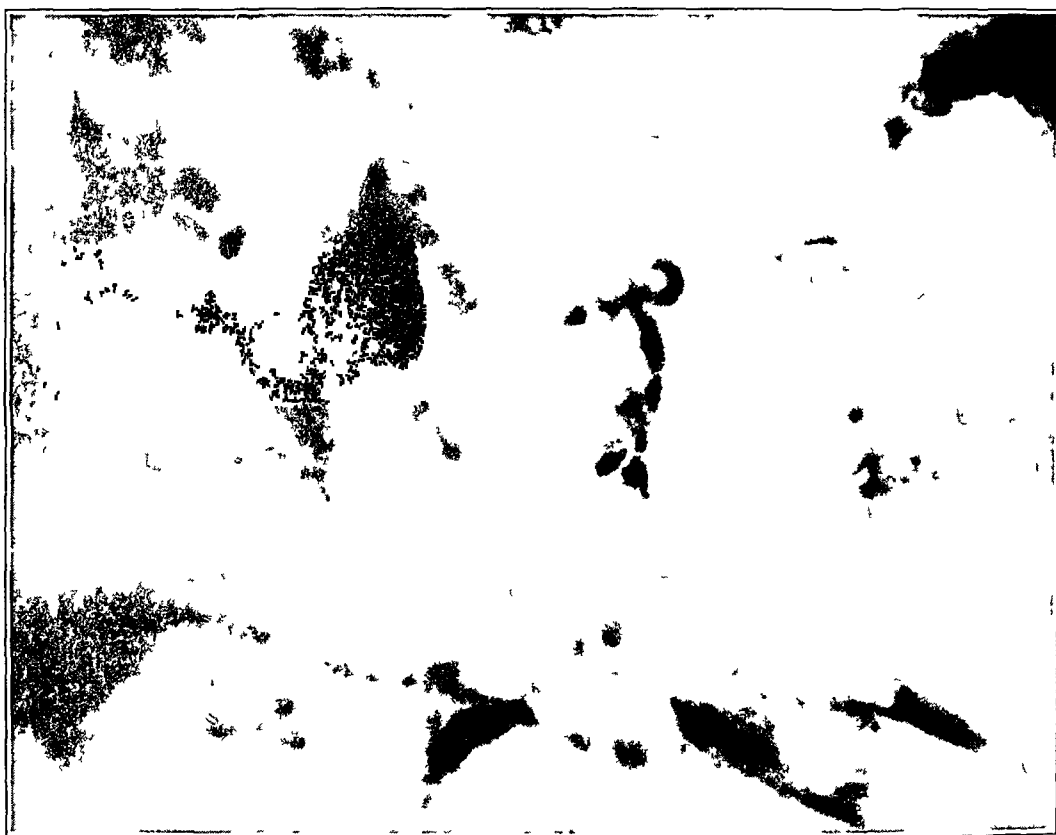


Fig 3—Photomicrograph of mixed adenoma (chromophobe and acidophilic) from case of "fugitive" acromegaly in which all elements have acidophilic type of Golgi net. Note large cell in center of field (magnification,  $\times 2,400$ )

the enlarged chromophobe elements characterizing the gland of pregnancy, which, because of their faintly acid-staining granules, many regard as arrested acidophils.

Chromophobe adenomas, while more commonly found in adults, occasionally occur in childhood under which circumstances their dual inhibitory effect on growth-promoting and sex-maturing elements is more clear. Such a case may now be cited for purposes of illustration.

THE CASE OF EVELYN D. *A pituitary dwarf with combined intrasellar craniopharyngioma and chromophobe adenoma, twice operated on for neighborhood symptoms. Observed over a period of eight years. Recent intramuscular injections of a growth extract with symptomatic benefit but no acceleration of growth.*

Dec 1, 1924 Admission of a 10 year old child (born Sept 27, 1914), with headaches and impaired vision

*History*—At the age of 3, she had fallen from a piazza and cut her forehead, with no apparent ill effects Apart from measles in her sixth year, she had been curiously exempt from the usual infections of childhood She had been a bright and studious child who was disinclined to play with other children

*Present Illness*—A year prior to admission, she began to fall off noticeably in her school work She was chided as being indolent, lazy and fat Six months later, she began having troublesome headaches, became constipated and had

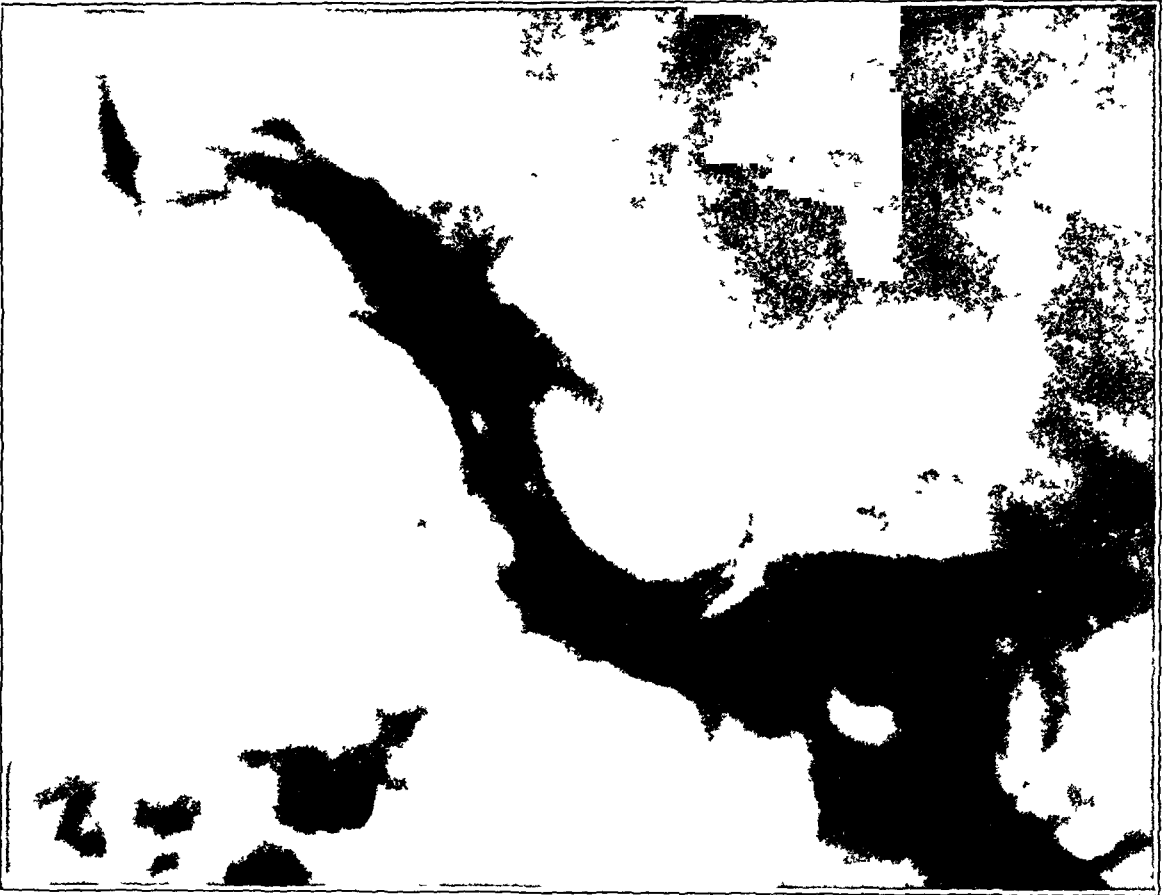


Fig 4—Expanded sella of Evelyn D in 1924 (natural size)

attacks of vomiting She grew sallow and lost weight in spite of her "puffy" appearance Recently there had been a noticeable failure of eyesight

*Examination*—This showed a placid and cooperative child, definitely undersized but apparently well nourished, teeth very imperfect, height 3 feet 11½ inches (120 cm, normal average for age, 131.5 cm), weight 49 pounds (22.2 Kg, normal average for age, 29 Kg) The skin was delicate, pale and shiny suggesting a nephritic edema, but the urine was normal The blood pressure was low, 85/45, the basal metabolic rate, —36 per cent

The neurologic survey disclosed a bilateral primary optic atrophy more marked on the left where vision was reduced to the perception of movements In the right eye there was 20/70 vision with an upper temporal field defect Roentgenograms showed a highly ballooned sella without shadows of calcification either within or above the expanded fossa (fig 4)

*Clinical Diagnosis*—Owing to the rarity of pituitary adenomas of any kind in so young a child, the typical syndrome of Frohlich was ascribed to a probable intrasellar, uncalcified hypophysial-duct (Rathke) tumor

*Operation*, Dec 19, 1924—Ether anesthesia A right transfrontal exploration disclosed a chiasm and optic nerves widely spread by a bulging though intact diaphragma sellae Suspecting a cyst, a needle was introduced, and 10 cc of a muddy, coffee-colored fluid containing cholesterol crystals was withdrawn The collapsed diaphragma was then incised, and a glistening sheath of tissue 2 by 3 cm in diameter representing the cyst wall was finally dissected out This done, a mass of soft, brownish, adenomatous tissue was brought to view, and after specimens had been taken for histologic verification, the cavity was thoroughly cleaned out by suction

The child made a good recovery from this operation (fig 5) Headaches ceased, vision was subjectively improved, and perimetric tests on Jan 1, 1925, showed definite widening of field peripheries By January 10, the fields were normal in both eyes and the visual acuity 20/20 in each The basal metabolic rate had risen twelve points, to  $-24$  per cent A series of x-ray treatments was given, and she was discharged Jan 16, 1925, greatly improved in all respects

*The Tissues*—1 The cyst wall proved to be typical of an hypophysial duct lesion 2 The adenoma was definitely of chromophobe type

*Subsequent Notes*—For the next twenty months, the patient was lost sight of, and in response to a letter of inquiry she finally reported on Oct 16, 1926, at the age of 12 years and 1 month Her height was then 127.2 cm the increment of 7.9 cm representing a slightly subnormal increase for a twenty month interval at her age (cf fig 10) She weighed  $58\frac{1}{2}$  pounds (26.5 Kg), an increase of  $9\frac{1}{2}$  pounds (4.3 Kg) The vision in the left eye, however, had fallen off to 10/200 with return of temporal hemianopsia and central scotoma

Two years more elapsed when, on Jan 26, 1929, she reported with the complaint of occasional headaches with beginning loss of vision in the left eye (aged 14 years, 4 months, height, 129 cm, weight, 28.6 Kg) During the next twelve months the symptoms slowly increased, and finally vision became so impaired she could make no further progress at school and her guardians were induced to have her reenter the hospital for further study

*Readmission*, Jan 30, 1930—The child, as at the time of her first admission, had become apathetic, inactive and inclined to remain in bed Both optic disks showed a high degree of atrophic pallor The fields showed bitemporal hemianopsia more marked on the left, with macular involvement Vision in the left eye was for movements only, in the right eye, 20/200 The child had grown 1.6 cm in the preceding twelve months The basal metabolic rate was  $-27$  per cent The sella was definitely enlarged over the previous entry

*Second Operation*, Feb 19, 1930—Under procaine hydrochloride anesthesia, the original flap was reelevated, and the suprasellar region reexposed without difficulty The diaphragma sellae had reformed and was bulging between the spread arms of the chiasm, it was electrically opened, and soft adenomatous tissue immediately began to extrude After fragments had been secured for supravital study and for fixation, the cavity was once more thoroughly cleaned out, masses of the large tumor being easily dislodged by the spoon and removed by suction, no trace of the former cyst was seen The margins of the incised diaphragma, having been drawn away from the nerves and chiasm until they rode free, were coagulated and infolded into the great cavity which would easily have held a large olive After complete hemostasis, closure was carried out with the usual detail

*Postoperative Notes*—The child behaved admirably during the operation, and there was no reason to expect trouble. On the late afternoon of February 20 and again on the afternoon of February 22, the flap had to be reelevated for an

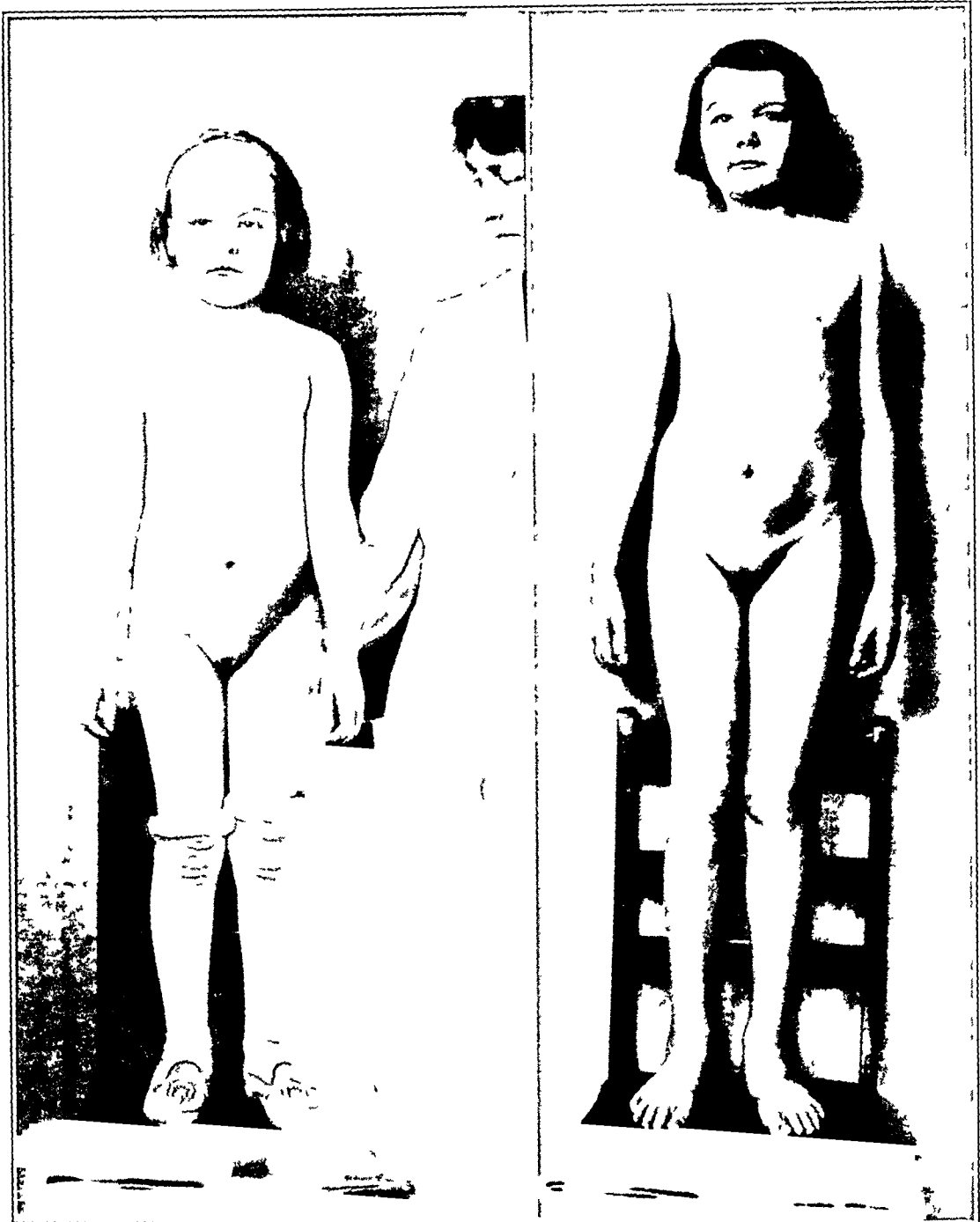


Fig 5—Evelyn D (standing on same chair) Left figure, shortly after first operation, Jan 6, 1924, aged 10 years, 3 months Right figure, Dec 19, 1932, aged 18 years, 3 months

extradural clot. There meanwhile was a marked hyperpyrexia (105 to 106 F), which fortunately soon subsided. Though these unfortunate surgical complications delayed convalescence, her visual fields rapidly widened, and by March 10 acuity

was so far regained that she was able to read small print, the main object of the operation was therefore attained. By the time of her discharge, on May 4, 1930, while more alert than she had been on admission, she was pale and bloated and had little appetite for food.

*Pathologic Note*—Supravital examination. The soft tumor was easily spread. The cells were typically of the large chromophobe type with delicately granular cytoplasm and large nuclei. Occasional multinuclear cells were seen and a single mitotic figure (fig 6). Fixed sections showed a chromophobe adenoma with considerable intercellular fibrous tissue ascribed to the former operation. No further mitoses were found.



Fig 6—Supravital preparation of chromophobe adenoma from Evelyn D, showing mitotic figure (magnification  $\times 850$ )

*Third Admission, June 13, 1931*—The patient reentered the hospital on request for the annual check on her condition. There had been little if any change. She was the same prim, laconic, undersized, well behaved child, with finely wrinkled and freckled skin (fig 7). Her age was 16 years, 9 months, weight, 30.4 Kg, height, 132.4 cm—a gain of 1.4 cm in sixteen months since the operation. The basal metabolic rate was —19 per cent. It had been our intention at this time to give her injections of a newly prepared growth extract, but its excess of protein content rendered this inadvisable.

*Experiences with Replacement Therapy*—Obviously what this child needed from the first was some form of effective substitution therapy, and before continuing with her story, our ineffectual experiences in

this direction may be recounted. As already mentioned, the attempt had been made in 1909 to overcome the acute postoperative cachexia that commonly follows total hypophysectomy of adult dogs, and we had even reported<sup>31</sup> what we thought were encouraging results following glandular implantations and the injections of crude bovine emulsions. Indeed, feeling that pituitary extracts might not be what is called species-specific, I had once transplanted the hypophysis taken from a still-born child into the brain of a man with an extreme degree of pituitary deficiency.

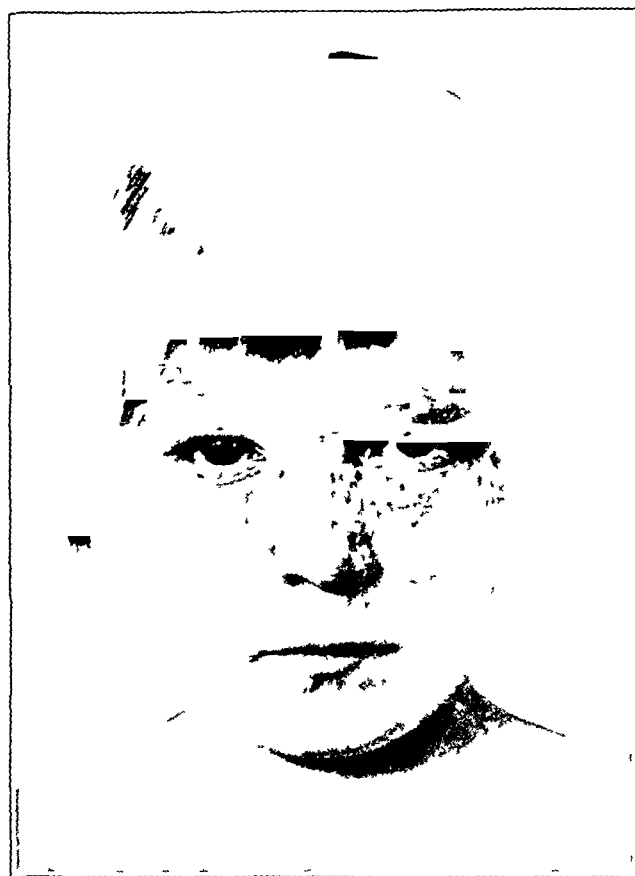


Fig 7—Evelyn D. at 18 years of age. Note persistent freckles on exposed areas of the otherwise pale skin, a characteristic of most hypopituitary cases.

This was done in accordance with Halsted's newly expressed formula<sup>63</sup> that glandular implantations would survive only in the presence of a physiologic deficit on the part of the host\*, but the case, as it turned out, was highly unsuitable for such an experiment, the patient's critical symptoms (produced by a craniopharyngioma) having been hypothalamic rather than pituitary. The brain was selected as the

\* These conclusions were based on experiences with parathyroid transplantations. Manley and Marine<sup>87</sup> showed a few years later that the parathyroid bodies readily survive autotransplantation in the absence of a physiologic deficit.

proper site for the transplantation on the assumption that the functioning gland required a neural environment

Dr Smith's subsequent success<sup>114</sup> (1927) in restoring immature hypophysectomized rats to a normal status by daily intramuscular implantation of fresh glands was based on the principle of absorption of what active secretion was already present in the tissue, without expectation that the implant might survive to produce more, no evidence of this ever having been observed. While it may therefore be unavailing, further efforts to secure a functioning pituitary transplant will doubtless be made, for theoretically it would provide the ideal form of substitution.

We were made acquainted with some of Dr Evans' early methods of preparing the growth hormone by one of his pupils, Mr Harold Teel, who entered the Harvard Medical School in 1925. In collaboration with Dr Tracy Putnam, a neutralized, dialyzed, potent and sterile extract was prepared,<sup>98</sup> armed with which we proceeded to elbow our way into the problem of experimental overgrowth. The prolonged intraperitoneal administration of the substance in dogs was found to cause what was looked on as the experimental counterpart of acromegaly.<sup>99 17 127</sup>

Encouraged by the effectiveness on animals of this sterile extract, in May, 1927, Dr Putnam gave seven successive intraperitoneal injections of 10 cc of the substance to the minute pituitary dwarf described in another place<sup>15</sup> as an example of hypopituitarism due to a craniopharyngioma. Each injection caused a prompt evacuation of the bowels with vomiting, in spite of which they were continued over a week's time as they seemed definitely to improve the child's appetite and general condition. A temporary febrile reaction following the last injection, however, led to their discontinuance.

During the following year, Drs Putnam and Teel<sup>124</sup> made some further improvements in their extract by salting out with sodium phosphate and succeeded, in getting a potent substance which was not only sterile but reasonably free from protein. Meanwhile, much time was expended in searching for a suitable chemical assay of potency by the study of metabolism and other ways, the most promising being based on the finding by Teel and Watkins<sup>125</sup> of a definite drop of the non-protein nitrogen following injections of the hormone in dogs, suggesting 'mobilization from the blood of substances needed for the building up of new protoplasm.'

It soon proved to be beyond the capacity of our laboratory to prepare the extract in sufficient bulk for our purposes, and Parke, Davis and Company through the agency of Dr E. P. Bugbee kindly agreed to come to our aid. They already had marketed an anterior lobe pituitary preparation (antuitrin) which one of my co-workers, Dr Davidoff, had tested (1924-1925) in rats without being able to detect the presence of the growth hormone, the only observed effect being an interruption of estrus. Subsequently adopting the improved Putnam-Teel procedure with some modifications in the way of a preservative,<sup>25</sup> they have prepared a series of substances which are sterile, give no protein reaction on injection, and contain a sufficient amount of the growth hormone to give prompt effects when tested on hypophysectomized rats.

During the summer of 1929, one of the early preparations of modified anterior lobe pituitary preparation (antuitin-G) was tested on three pituitary dwarfs ranging from the ages of 19 to 30 all with open

epiphyses They received daily intragluteal injections of 5 cc without appreciable effect, and on retesting the substance on rats, it was disappointingly found to have lost its growth-stimulating effect, possibly because of the nature of the preservative added to it A more potent anterior lobe pituitary preparation which retained its activity was subsequently prepared, and to give this a reasonable trial Evelyn D was readmitted to the hospital

*Fourth Admission*, March 7, 1932—During the twelve months' interval, normal vision had fortunately been retained, but the patient had lost ambition, spent most of her time in bed and was too indolent to go to school This may in part have been due to consciousness of the increasing disparity between her age—she was now 17½—and her size While her height (cf fig 10) had slowly increased (from 120 to 134 cm) in the seven years she had been under observation and her weight had perceptibly jumped after each of the operations (cf fig 11), even this had remained stationary for eighteen months Her epiphyses on x-ray films still resembled those of a child of 8 or 9 years The blood pressure remained low, 90/60, also the basal metabolic rate, —18 per cent

In view of the child's marked inappetence, preliminary studies were made of the calories she would normally consume on as appetizing a diet as could be provided, 964 calories was the highest she could be prevailed on to take Meanwhile, the more potent anterior lobe pituitary preparation was tested intradermally and subcutaneously to exclude the possibility of a foreign protein reaction, and on March 16 she was given her first daily intramuscular injection of 2 cc The effect on her appetite was immediate Her measured calories on the second day were 1,285, on the third, 1,356, on the fourth, 1,466, and she was soon taking 1,600 calories *per diem* Meanwhile, her appearance and activity were noticeably improved \*

The injections, which were continued for one hundred and ten days, were stepped up to 3 cc on April 4 and to 4 cc on May 20 She had by this time become so unusually alert and active she was a constant source of surprise to her relatives, and to keep her occupied she finally was given a position as a messenger girl in the ambulatory clinic

She had gained in three months, from March 16 to June 28 when finally discharged, from 30.5 to 35.5 Kg, which almost equaled her gain (8 Kg) during the preceding seven years It was very difficult to be equally certain about her measured increase in height (from 134 to 135.5 cm), for she stood more erect and variations of a centimeter or two occurred from day to day

This, then, may be taken as a representative picture of dual hypopituitarism involving both factors of sex and growth, and the slow accession of growth the child has shown is ascribable to what remnants of the normal gland, relieved of pressure, have retained some degree of activity Certainly the preparation of growth hormone, either from insufficient dosage, from too long delay in its administration or too short a time given to it, has shown no appreciable effects on the plotted graph

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\* Her blood studies, taken on March 8, had shown a nonprotein nitrogen of 15.07 mg per hundred cubic centimeters, with a urine elimination for the twenty-four hours of 2.98 Gm Corresponding studies made after the injections had been started showed a blood nonprotein nitrogen of 32.08 mg per hundred cubic centimeters and a urine elimination of 5.56 Gm



(cf fig 10) And though there was an acceleration of weight and a definite improvement in the child's general condition, her weight (cf fig 11) quickly dropped off on cessation of the treatment, in full conformity with what happens to laboratory animals when the daily administration of the growth hormone is interrupted

The preparation of anterior lobe pituitary preparation which was employed was markedly potent when tested on a dwarf rat, whose weight had remained unchanged for more than a year after hypophysectomy. It, however, is obviously far from the ideal product necessary for effective substitutional therapy. Engelbach has recently (1932) reported<sup>45</sup> the case of a female pituitary dwarf 9 years of age who received over a period of eight and a half months subcutaneous injections of 9 cc of a purified Evans growth hormone, during which period an increment of  $2\frac{7}{10}$  inches (6.75 cm) in height and a gain of  $7\frac{1}{2}$  pounds (3.45 Kg) in weight were recorded.

Reichert failed to observe<sup>105</sup> (1928) any effect on the growth of a puppy to which from the seventh to the eleventh month after hypophysectomy daily subcutaneous injections of the minced pituitary gland of a rabbit had been given. The only response was an imperfect sexual maturation with continued estrus, the failure to stimulate growth was ascribed to probable closure of the epiphyses. I, however, am informed by Dr. Evans that by the injection of 25 to 40 cc daily of the more highly purified growth hormone he has recently described,<sup>40</sup> which is essentially free from the sex principle, it has been possible to bring about normal growth without acromegalic manifestations in a puppy hypophysectomized<sup>106</sup> by Dr. Reichert at eight weeks, treatment having been begun four weeks later.

While we may any day expect revelations in regard to this important matter of substitution therapy for dual hypopituitarism, the large amounts of the most effective known extract that must be intraperitoneally injected day after day effectively to compensate for the deficiency in experimental canine hypophysectomy precludes its clinical use, and the daily implantation of glands taken from the same species, so effective in dwarfed rats,<sup>114</sup> is unfortunately inapplicable to human beings.

*Growth and Sex* —Why should Nature have given to the pituitary body the control of two such important but, so far as can be seen, wholly unrelated activities as that pertaining to growth and that essential to reproduction, which more appropriately might have been controlled from a more caudal station? One would assume that they must somehow work together, for very similar nervous impulses must act on them, and the fact that adolescence normally occurs during a period of very rapid growth would suggest that they at least do not work in opposition as some of the early experiments with the injection of growth extracts had suggested.<sup>52</sup> The therapeutic problem of the dwarfed child whose case has just been cited would have been simplified had the deprivation syndrome not been dual but consequent on the loss of either hormone by itself.

For want of any known agent capable of destroying or inactivating one type of secretory cell while the other is left intact, the possibility of studying by experiment the deprivation effects of either element singly is precluded. That such conditions, however, at least so far as the acidophils are concerned, may occur spontaneously has been shown by Smith and MacDowell,<sup>117 118</sup> who have made the surprising discovery that a defective gene has led to a congenital absence of acidophilic elements in the hypophysis of the hereditarily dwarfed mice of the Dunn strain. In these animals the growth principle alone is suppressed, leaving the gonadotropic hormone essentially unaffected else there could be no continuance of the species. Should it prove that all the elements of the adenohypophysis of these dwarfed mice possess a Golgi apparatus invariably of basophilic type, while that carrying the factor of growth to the acidophilic cells is lost, it will be of even greater interest from the standpoint of genetics. But even as they stand, these important observations indicate that the hormones of growth and sex have a separable rather than interdependent action.

Growth in the abstract is a highly mysterious process. It can unquestionably be checked by pituitary insufficiency, however brought about, or stimulated by administering the appropriate pituitary hormone. At the same time, it is well known that an inadequate diet and unhygienic surroundings may similarly impede a child's growth just as a change from unfavorable to more favorable surroundings where sunshine, fresh air and better food are plentiful may stimulate it. What if anything has the pituitary body to do with this? My friend, Dr. L. B. Mendel, a few years ago informed me that by an improved diet alone he could produce rats as large as those given pituitary injections, and suggested that the question be put to the test.

Accordingly, Drs. Bryan and Gaiser,<sup>24</sup> basing their study on the number of days required for 60 Gm. rats to attain a weight of 200 Gm., found that those on an ordinary diet for control purposes required an average of 50 days, those on Mendel's special growth diet required an average of 38 days, those on an ordinary diet supplemented by growth hormone required an average of 37 days, while those on Mendel's special diet supplemented by hormone injections required an average of only 28 days—a growth rate of 6 to 7 Gm. *per diem* which they regarded as the maximum attainable.

Polyphagia, as is well known, is a symptom of acromegaly, and dogs when injected with growth hormone become ravenous eaters. So, in the attempt to interpret these experiments, the question immediately arose as to whether the injections merely served to increase appetite or whether they actually stimulated growth by somehow making the nutriment more available as a building material.

We subsequently learned from Dr. Mendel that his co-workers, Anderson and Smith, had prepared a still more effective diet through which in the rat an average daily growth of 7.3 Gm. might be attained. And feeling that Dr. Mendel was not as yet convinced of the efficacy of the growth-promoting hormone by itself, we determined to see whether diet alone could effect the size of totally hypophysectomized rats whose weights never exceed that of the preoperative level. It was

found that the improved diet had no influence in starting growth. However, so soon as the administration of the growth hormone was begun, the animals promptly began to gain weight with a rapidity proportionate to the excellence of the different diets employed. On the other hand, cessation of the daily injections of the hormone was promptly followed by a loss of weight irrespective of the quality of the diet.

These experiments appeared to us to show the superiority of the hormone to diet as a growth-promoting influence, though they have left the question of appetite unanswered, for they were complicated and difficult enough to carry through without attempting to determine the precise number of calories the more rapidly growing rats consumed in comparison with those which grew more slowly.

It has been customary, as we have just seen, to measure the growth of four-footed laboratory animals in terms of weight, and the published graphs<sup>53</sup> consequently are difficult to transfer to the clinic with its plantigrade subjects whose measured erect height is the basis of registration. The closest parallel we have to what experimental gigantism in lower animals might be like if produced by a chemically pure hormone of growth is the exaggerated height occasionally attained by young persons in the period before epiphysal closure normally occurs. While it is not easy to determine just where overgrowth of this kind ceases to be merely excessive and becomes pathologic, I may cite two examples of patients at the present time under observation—both of them young normally adolescent lads, of whose rapid increase in stature records have fortunately been kept over a period of five to six years.

**THE CASE OF JOHN J.** This boy, now 16½ years of age, was born July 17, 1916, weighing 7½ pounds. As a child he was always considered to be somewhat undersized, but suddenly at the age of 8 he began to grow with unusual speed. Precise records unfortunately were not kept until two years later, but in the five years between March 26, 1927 (10 years, 8 months) and Jan. 2, 1932 (15 years, 6 months), he grew 36 cm. at the almost constant rate of something over 3 inches (7 cm.) a year.

When he first came under observation in September, 1931, he was found to be a normally proportioned, adolescent youth 6 feet, 4¾ inches (192 cm.) tall, and with a span 7 cm. greater than his height. His weight was 202 pounds (91.8 Kg.). Roentgenograms of the skull showed large accessory sinuses (fig. 8) and a suspiciously large sella which measured 14 by 17 cm. The long bones were normal in appearance with open epiphyses. His basal metabolic rate was normal. His blood pressure was 110/70.

No treatment was recommended, and the boy's parents were encouraged to look on the condition as indicating nothing abnormal. However, three months later, in January, 1932, he was brought in again because of the complaint of headaches and eye strain. What was taken to be early evidences of upper bitemporal defects in the visual fields were disclosed, and, fearing that after all he might conceivably have a pathologic hyperplasia of acidophilic elements, the pituitary gland was irradiated. During the next three months there was no measurable increment of growth when it again began to move up, and in July, 1932, the gland was again subjected to irradiation.

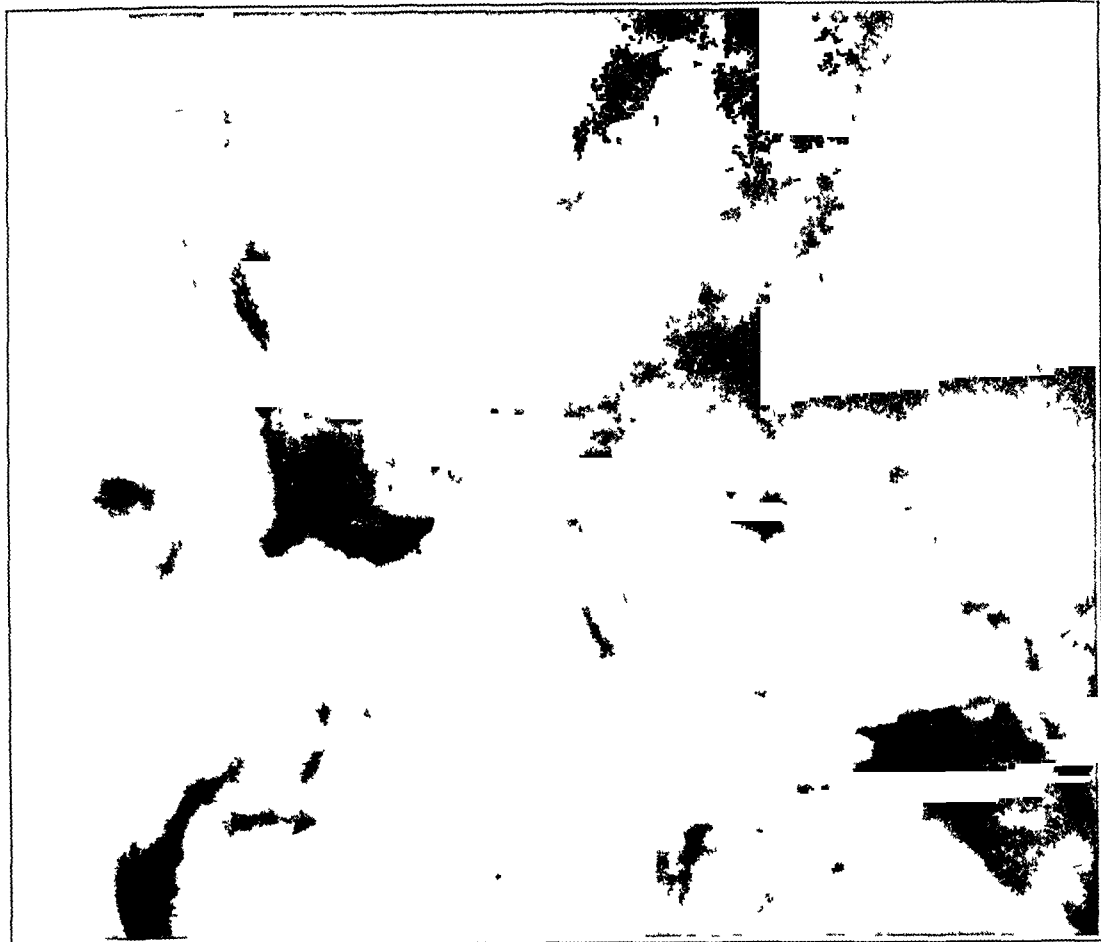


Fig 8—The slightly enlarged pituitary fossa in the case of John J (natural size)



Fig 9—The small (for size of skull) pituitary fossa and large sinusoidal spaces in the case of Charles D (natural size)

In the twelve months which have elapsed since the first of these radiotherapeutic sessions, there has been a growth of only five eighths of an inch instead of the yearly increment of 3 inches which his carefully plotted curve of growth would have led one to expect

**THE CASE OF CHARLES D** This boy, an orphan, born May 20, 1917, had been a frail and undersized child with a congenital dislocation of the lens in each eye, fortunately correctable by glasses. At the age of 7, he suddenly began to grow with great rapidity and when first seen, Oct 17, 1927, at 10½ years of age, he was said to have grown 4 inches in the preceding twelve months and to have gained 60 pounds (27.2 Kg) in weight

He presented a not unfamiliar endocrinologic problem suggestive of adiposogenital dystrophy combined with overgrowth. Roentgenologic studies showed a disproportionately small sella (fig 9), large accessory nasal sinuses, an area of calcification in the region of the pineal gland and normally open epiphyses. No treatment was recommended, and his guardians were advised to let him work out his own salvation. That he was genetically entitled to be tall was indicated by a family history of tall forebears on both sides of his family and by his having an elder brother who measured 6 feet, 2 inches in height and weighed 250 pounds.

Five years elapsed, when on Oct 20, 1932, he again came under observation. He was then 15½ years of age, had passed through a normal adolescence, had lost his adiposity and become a spindling youth 6 feet, 7½ inches (201.8 cm) tall. A careful record of his height and weight had fortunately been kept by his family physician, Dr R J Carpenter, who during 1929 had found the boy to have glycosuria and low blood pressure (98/70), but these symptoms had spontaneously disappeared.

To see whether the excessive growth might be checked, as it appeared to have been in the preceding case, the hypophysis was irradiated under Dr Sosman's direction six months ago. Since then, there has been no measurable increment in stature—a short time, to be sure.

On the accompanying graph (fig 10), the growth of these lads has been carefully plotted with precise attention to the detail of the month of age at which the recorded measurements were taken, and the curve is a surprisingly regular one. It can be seen that their stature far exceeds the extreme upper limits of accepted heights for males of their age.<sup>4</sup> The x-ray treatments were given partly on the grounds that radiation is known to have a definitely inactivating effect on the growth-promoting adenoma of acromegaly and partly because the prolonged x-ray treatment of a brain tumor of a young girl had inhibited her growth when compared with that of her identical twin sister. Whether the knuckle and plateau shown in the growth curve of these boys was caused by, or fortuitously coincided with, the radiation remains uncertain for want of such a control as would be deemed necessary in laboratory experimentation. The weight of John J has not been taken

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<sup>4</sup> The normal average height for males and females with the upper limit for males and lower limit for females in the shaded areas of the chart are plotted from Professor Bardeen's detailed figures recently prepared for the Child Conference in Washington.

with the same regularity as his height, but he had always been a normally proportioned youth with a proper height-weight ratio. Charles D, on the other hand, whose weight and height have always been taken together, has shown (cf fig 11) extraordinary fluctuations in weight as taken by different observers even though his progressive increment of height meanwhile remained unaffected.

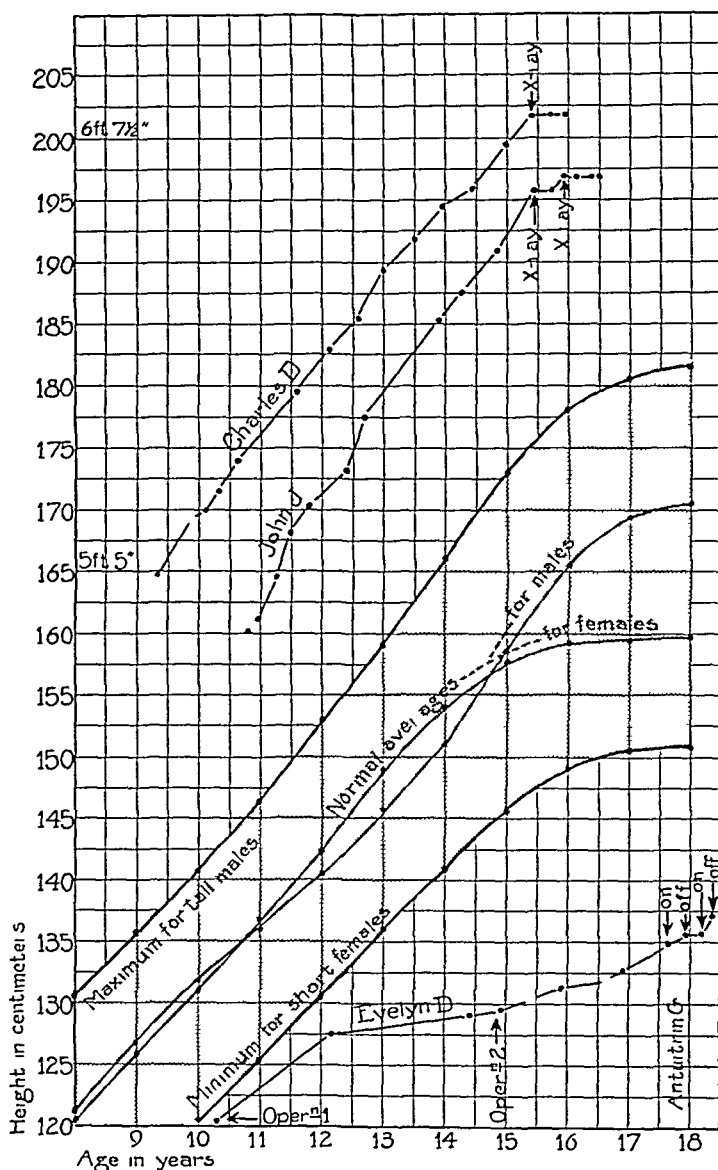


Fig 10—Height-age curves of Charles D, John J and Evelyn D, compared with normal averages in shaded areas

What, in terms of pituitary function, can be said of these overgrown 15 year old, normally adolescent boys? Are hereditary influences involved? Is their unusual height ascribable to a growth-stimulating diet with present-day attention to vitamins, or to an overactive pituitary gland, or possibly to the two in combination?

While precise figures are difficult to get at and properly to appraise when secured, it is a matter of common observation in recent years that children tend to be taller than their parents. Recalling that when I was a college undergraduate an anthropologically minded gymnasium director had annually made detailed measurements of all students—a custom which has since been continued—I have from this source obtained the comparative figures relating to the single factors of age and height of the present freshman class and that of forty years ago. Similar

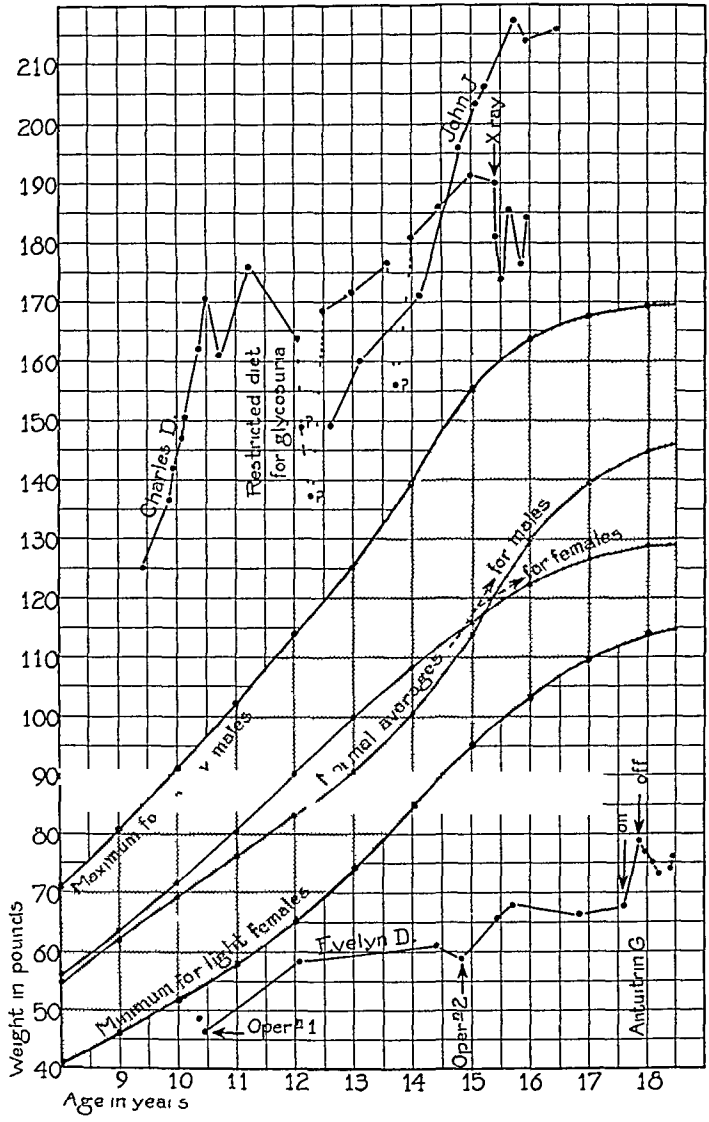


Fig 11—Weight-age curves of Charles D, John J and Evelyn D, compared with normal averages in shaded areas

figures have also been obtained from two other New England colleges. As it turns out, the average age (*viz*, 19½) of freshmen in 1892 was a year older than that (*viz*, 18½) of the freshmen in 1932, from which, all other things being equal, those of forty years ago should more nearly have attained their full stature.

The combined figures of the three institutions, however, show that only 5.67 per cent of the freshmen in 1892, in contrast to 19.47 per cent of the present, 1932, freshmen, were 6 feet or over. In other words, forty years ago *circa* one out of

every twenty matriculating students was 6 feet or over (the tallest 6 feet, 4 inches) whereas today *circa* one out of every five (the tallest 6 feet, 7 inches) is 6 feet or over

## 2 THE ACIDOPHILIC ADENOMAS AND THEIR SYSTEMIC EFFECTS

Let us now turn to the consideration of pathologic overgrowth as represented in gigantism and acromegaly. Both conditions are now known to be associated with an adenoma the preponderance of whose elements in the active stage of the disorder show acidophilic granules.<sup>12</sup> This fact has provided the most dependable evidence at hand that the growth hormone actually is a product of these cells, and it is now made more certain by the recent disclosure I have mentioned<sup>117</sup> regarding the absence of acidophilic elements in the pituitary glands of hereditarily dwarfed mice.

But if clinical gigantism and acromegaly are an unadulterated expression of overactive acidophilic elements resulting in an excess of growth hormone alone, why should these states so often be accompanied by dystrophic changes in the reproductive apparatus? It will be recalled that Evans' giant rats, and the acromegalic dogs produced in my laboratory, became not only overgrown but sexually dystrophic in the course of the experiment, but in neither laboratory was there then available a growth extract uncontaminated by the sex-maturing principle. And so far as the clinical disorders of like kind are concerned, reference has already been made to the fact that a growing adenoma composed of one type of cell may in time through compression destroy the functional activity of the remaining normal elements in the gland.<sup>65</sup>

So for want of a simon-pure growth hormone, it is impossible to say with certainty whether excessive growth can be experimentally produced without associated gonadal effects. Nevertheless, what clinical evidence we have points in that direction. It is strongly suggested by the fact that in many acromegalics the evidences of sexual dysfunction are long delayed, and when the adenoma is too small really to expand the sella, there may, for example, in affected women be no interruption whatsoever of the normal menstrual cycle. Child-bearing, however, is apt to have a pronounced effect in activating the malady—an effect conceivably brought about by the increase of the growth hormone required for the needs of the child and acting at the same time deleteriously on the mother. In this connection, attention may be again called to the suspicion that the Erdheim-Stumme "pregnancy cells" are enlarged chromophobe elements arrested in the course of becoming fullblown granular acidophilic cells of usual type.

In the clinic we must take into account other factors than height and body weight when considering pathologic overgrowth. The acromegalic's stature may even become shorter owing to the immobility of



his thickening vertebrae, while at the same time he disproportionately gains weight. This in part is due to an increasing heaviness and solidity of the bones, in part to the peculiar "edema" of the connective tissues, but more particularly to the disproportionate increase in the size of the visceral organs.

To this feature of the disease—the splanchnomegaly—special attention was drawn in a report with L. M. Davidoff on the postmortem findings in four cases.<sup>40</sup> While it is not so apparent in experimentally induced overgrowth in the rat, splanchnomegaly in the dog after the prolonged administration of growth extracts may be extreme. Whereas the weight of one of our injected animals at the expiration of eighteen months was almost double that of the litter-mate control, the liver of the former was approximately three and one half times as large—an increment far greater than could be explained by the fatty infiltration and passive congestion that was present.

To what can this hypertrophy be ascribed? To an increase in the size of the cells or in their number within a given hepatic unit, or are the number of hepatic units actually increased? Or again, is the enlargement merely due to that sort of connective tissue thickening or edema which causes the puffiness of the cutaneous and subcutaneous tissues? To these questions there is as yet no wholly satisfactory answer.

It would be of little avail to include here the report of a typical case of acromegaly for its features are well known. It, however, is far from being a disorder which affects all its victims in the same way or in equal degree. The following case, which at the present writing is a source of anxiety, may serve as well as any other to show how complicated may be the syndrome and how great may be the difficulties of interpreting the secretory aspects of acidophilic hyperpituitarism in terms of experimental overgrowth in animals, particularly when they become masked and overlain by pressure involvement of the intracranium.

*THE CASE OF MRS. E. L. Postpartum amenorrhea. Continued lactation. Fugitive acromegaly. Enlarged sella with neighborhood symptoms demanding operation. Chromophil adenoma. Subsequent pressure symptoms improved by irradiation. Ultimate symptomatic involvement of hypothalamus from intracranial expansion of tumor.*

Elizabeth L., born in 1893, with an excellent heredity and good general health, married a government official in 1917 when 24 years of age and went to Shanghai to live. She passed through her first pregnancy in 1919 without mishap. A second child, born a year and a half later (November, 1920), was similarly breast fed, but when weaned, at the expiration of twelve months, lactation continued in spite of all efforts to check it. Meanwhile, in the fourth month postpartum (March, 1921), normal menstruation had been resumed and continued for twelve months, when it ceased permanently.

In spite of the continued amenorrhea and persistent lactation, she regarded herself as well until November, 1925, when she began to have severe headaches with blurring of vision, and soon the sight in her right eye became seriously impaired.

Roentgenograms at this time disclosed an enlarged sella. At this juncture (December, 1925) a gynecologist explored the pelvis and, finding the ovaries in "a state of senile atrophy," split them sagittally and implanted under the peritoneum the supposedly normal ovaries from another patient.

On the patient's return to America for a visit the next year (1926), her parents were dismayed at her acromegalic appearance. She was still lactating profusely and troubled by excessive sweating. Not only had she gained some 40 pounds (18.1 Kg) in weight, but she was distinctly exophthalmic, and her features had become coarse, hirsute and grossly enlarged with thick nose, lips and tongue. The ophthalmoscope disclosed a primary optic atrophy with definite haziness of the disk margins but no measurable swelling. Bitemporal field defects indicated

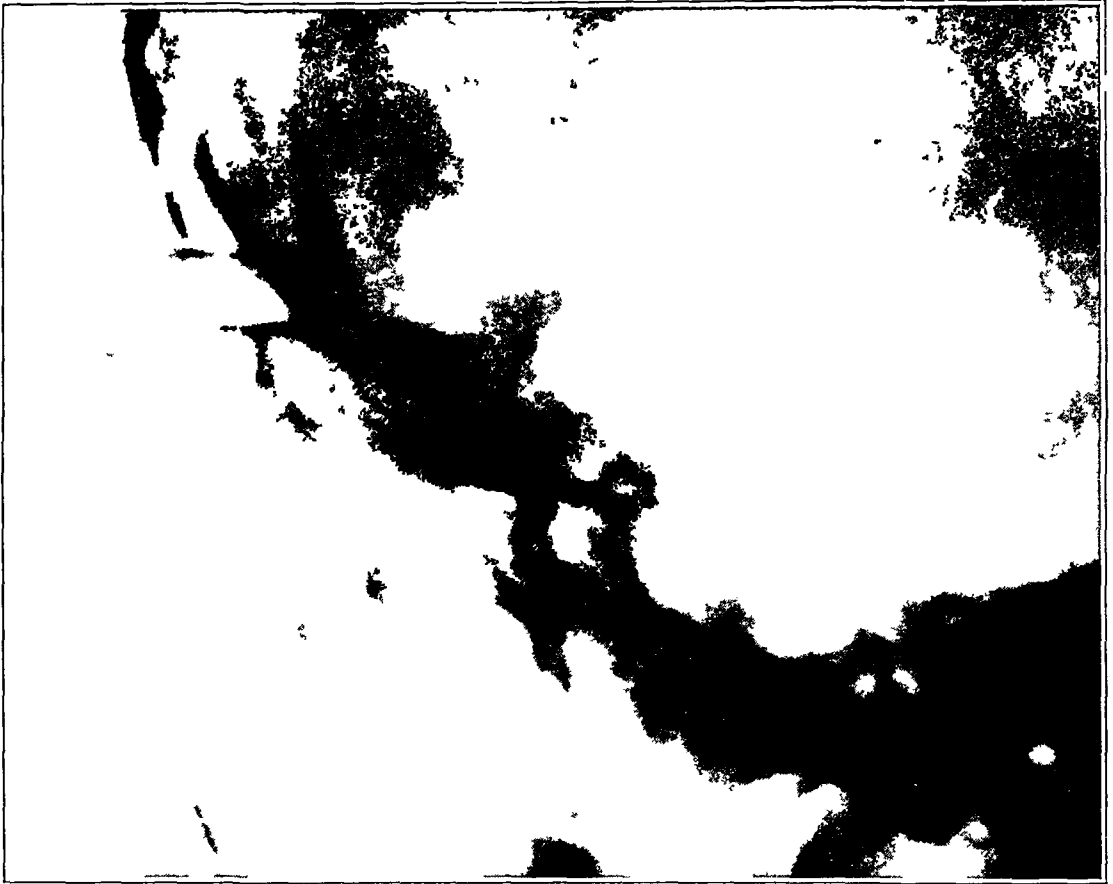


Fig. 12—The ballooned sella in the case of "fugitive" acromegaly with prolonged lactation (natural size)

involvement of the chiasm by tumor, visual acuity in the right was reduced to appreciation of finger movements. Roentgenograms showed the phalangeal tufting characteristic of acromegaly and an expanded sella (fig. 12). The metabolism was  $-2$ , blood pressure, 110/65, height, 166 cm, weight, 78.5 Kg.

To preserve vision, a transphenoidal operation (this being the procedure favored at the time) was performed (August, 1926), and as much as possible of the soft intrasellar growth was removed. The tissue showed cells of acidophilic type with alpha granules (Bailey) scattered among large chromophobe elements. From this operation the patient made a good recovery, with temporary cessation of headaches and improvement in vision. Active lactation, however, persisted, and she continued to gain weight, which by November reached 194 pounds (88 Kg).

She reentered the hospital in February, 1927, because of a return of severe headache with occasional attacks of dizziness and projectile vomiting. Lactation and excessive sweating still persisted, and she at times was unduly somnolent. There was an unmistakable low grade of papilledema, particularly marked on the left. Her teeth which had become greatly decayed were extracted at this time at her insistence, and the pituitary region was thoroughly irradiated. This was followed by prompt subjective improvement and disappearance of the headache. There was a gradual diminution of lactation, which by November, 1927, had practically ceased, and though she had continued to gain weight up to 200 pounds (90.7 Kg.), her acromegalic appearance had noticeably lessened.

In February, 1928, her health was so greatly improved that she returned to Shanghai, and for the next eighteen months felt exceptionally well, though the amenorrhea persisted. In June, 1929, and again in September, 1929, she had a convulsive seizure with unconsciousness and incontinence of urine. In March, 1930, she began having peculiar momentary petit mal seizures with a "rush of blood to the head" and uncontrollable evacuation of the bladder. Apart from finding herself wet, the patient had no knowledge of these attacks and showed a curious disregard of them. Severe headaches from which she had been free for nearly three years again appeared with failing sight and hypersomnia. She was annoyed by a bruit synchronous with the pulse, which could be stopped by pressure on the neck. A series of x-ray treatments was given, and she was sent back to America, but before her arrival all these symptoms had disappeared, and there had been a marked improvement in vision.

On her readmission to the hospital (April, 1930) she was in good spirits, looked well and was symptom-free. Apart from haziness of the margins of the somewhat pale disks with measurable swelling of one diopter, the examination revealed nothing noteworthy. In June, 1930, she was given further roentgenotherapeutic treatments, and two months later she rejoined her husband in China. There for the next year and more she led an active life and felt reasonably well in spite of occasional petit mal seizures described as trances in which she would void involuntarily.

By January, 1932, the seizures began to grow more numerous and severe and in August, 1932, she returned again to America. On readmission to the hospital for study, she appeared in better general condition than at any previous time. Though still heavy (198 pounds [89.8 Kg.]), her acromegalic appearance was scarcely noticeable. The papilledema had disappeared, the visual fields were wide, visual acuity had improved. The blood pressure was 108/72, metabolism, — 11 per cent, there was no polydipsia or polyuria.

The peculiar attacks appeared to come in waves with intermissions of two or three weeks. They were characterized by a bright flush of face and neck with a profuse sweat and involuntary evacuation of the bladder. They so strongly suggested the autonomic (parasympathetic) stimulation brought about by hypothalamic irritation<sup>37</sup> it was finally decided to take ventriculograms. These were finally made (December, 1932) and showed a marked hydrocephalus with a filling defect of the third ventricle.

At this point, the story of the patient begins to get beyond the bounds of the present discourse. The prior history briefly summarized is that of a woman with mild acromegaly coming on after parturition with prolonged lactation, persistent amenorrhea and early evidences of intracranial pressure long unaccounted for and due, as finally shown

to the suprasellar projection of an acidophilic adenoma into the third ventricle with resultant hydrocephalus and hypothalamic (autonomic) fits

Fully to unravel the symptomatic effects of this lesion, while possible, is unnecessary here. There are, however, a few points to which special attention may be called

1 The acromegalic symptoms of overgrowth shown by the patient were "fugitive"<sup>11</sup> and the adenoma, while acidophilic in type, was composed chiefly of large, undifferentiated chromophobe elements. It is not inconceivable that it may have been an adenoma arising from the "pregnancy cells" which, as already stated, may be chromophobe elements arrested in the process of ripening into acidophils. The human pituitary body of pregnancy, when transplanted into immature mice, has been shown by Philipp<sup>95</sup> to have temporarily lost its sex-maturing capacity, which would seem to indicate that the sex-maturing substances in the urine of pregnant women and in the placenta must come from some other source.

2 Whether the cells of the patient's tumor secreted a lactogenic hormone corresponding to the "prolactin" of Riddle<sup>109</sup> could only have been determined by testing the effect, on the previously sensitized mammary glands of animals, of implanted tissue taken from the growth. Both Riddle<sup>110</sup> and Evans<sup>53</sup> feel assured that the adenohypophysis provides such a hormone definitely separable from the principles influencing growth and sex. If that is so, it was probably present (together with other impurities) in the early preparations of the growth hormone, for Putnam's acromegalic dogs showed hypertrophic, lactating mammae. Conversely, Collip and his co-workers<sup>28</sup> have just shown that hypophysectomy of a rat after parturition leads to a prompt retrogression of the mammary glands with cessation of lactation.

3 In view of what is to follow in describing pituitary basophilism, it will be noted that the patient's blood pressure was invariably subnormal which may in this case, as in chromophobe tumors, be ascribed to pressure obliteration of the neurohypophysis, and, similarly, her amenorrhea may be attributed to the compression effect of the large tumor on the cells (whatever they may be) that elaborate the luteinizing principle. The skin was pale, coarse, moist and without striae, and the adiposity was generally distributed and not confined to trunk and face.

4 The patient's periods of somnolence as well as the adiposity might conceivably be looked on as of hypothalamic origin, but both are frequently seen in cases of pituitary disease which does not involve the interbrain, and they were unassociated with polyuria. The temporary seizures appear to have been stimulatory episodes comparable to those described by Penfield<sup>94</sup> in the case of a patient with a proven third ventricle cyst.

### 3 BASOPHILIC ADENOMAS AND THEIR SYSTEMIC EFFECTS

So far, very little has been said of the hormone of sex other than that the mechanical effects of chromophobe adenomas of childhood produce a dual deficiency that inhibits both growth and maturation.

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<sup>9</sup> This is not to be confused with the long known galactagogue effect of posterior lobe extracts.

For the same reason, the acidophilic adenoma of acromegaly may in time so compress the residual normal elements that sexual dysfunction is superimposed on the primary symptoms of overgrowth. This at least is the most probable explanation.

While evidence that the growth hormone comes from the acidophilic elements now appears to be conclusive, the attribution of the sex principle to the basophils is still under debate. There have been a few highly suggestive observations in its favor. One of them was the Smiths' <sup>120</sup> demonstration (1923) that the central core of the bovine anterior lobe where basophilic cells abound possesses a greater sex-maturing potency than does the rim where acidophils predominate. Another was the identification by Addison <sup>1</sup> of the so-called "castration cells" as basophilic elements. This in turn was followed by Engle's discovery <sup>40</sup> (1929) that the gland of the castrated rat not only shows a multiplication of these elements but acquires increased potency as a sex-maturing agent, as shown by its effects when transplanted into immature mice.

This reciprocal reaction of Engle proves, however, not to be true of all species. Severinghaus <sup>113</sup> has shown, for example, that castration increases the sex-maturing capacity of the guinea-pig's hypophysis without demonstrable increase of the basophils. What is more, in man and some other mammalian forms, it is the acidophils that appear to be increased in castrates. On the other hand, it is said that in the rutting season and in animals (e. g., the marmot <sup>101 102</sup>) emerging from hibernation, the number of basophilic cells are augmented, but in view of the known species variability and seasonal variation in the number of these elements, observations of this sort are difficult to appraise.

Furthermore, the quota of basophils is said to be greater than normal in certain clinical disorders, such as vascular hypertension and the uremic stage of renal disease, and I am inclined to believe that the same thing will be found true of eclampsia. More recently, Zondek has reported <sup>137</sup> that the pars intermedia, pars nervosa and stalk of the human (but not of the bovine) hypophysis contains a follicle stimulating substance (prolan A) which he ascribes to the inwandering basophilic elements.

Now it has been recently brought to light that a well recognized polyglandular disorder—in the same sense, to be sure, that acromegaly is polyglandular—not infrequently is associated with a pure basophilic adenoma of the anterior pituitary <sup>38</sup>. Were it not that adenomas of this type have been thought to be exceedingly rare and of no pathologic significance, this disclosure would not have seemed so highly peculiar, and the patients with the disorder would continue as in the past to be looked on as the victims, for example, of osteomalacia, of hypertension or of diabetic obesity.

The external evidences of the disorder are unmistakable when once pointed out, and the accompanying photographs will show how rapidly it has developed in the course of a few months in the young girl, Alice D., 15 years of age, to whose case attention has elsewhere been

drawn<sup>39</sup> The symptomatic features of the malady (not yet verified, to be sure in this particular instance) are subjoined

There was a precocious adolescence, at 10 years of age, associated with normal menses which continued for three years and abruptly ceased She acquired a peculiar plethoric appearance with an abnormal growth of hair on brows, lip and chin (fig 13) She became increasingly abdominous with progressive increase of purplish striae atrophicae (fig 14)

She has had persistent backache and become round shouldered with the loss of 4 cm in measured stature, due undoubtedly to the roentgenologically evident decalcification of the vertebrae and an abnormally high calcium elimination A spontaneous fracture of the pelvic bone, evidently in a tumor, has healed with callus formation



Fig 13—Facial hirsuties in a case of pituitary basophilism at 15 years of age

She has a subnormal basal metabolic rate, a lowered tolerance for carbohydrates and a high blood pressure, presumably indicating secondary involvement or imbalance of other glands — parathyroid, thyroid, pancreatic islets and adrenal—to almost any one of which the syndrome might have been ascribed

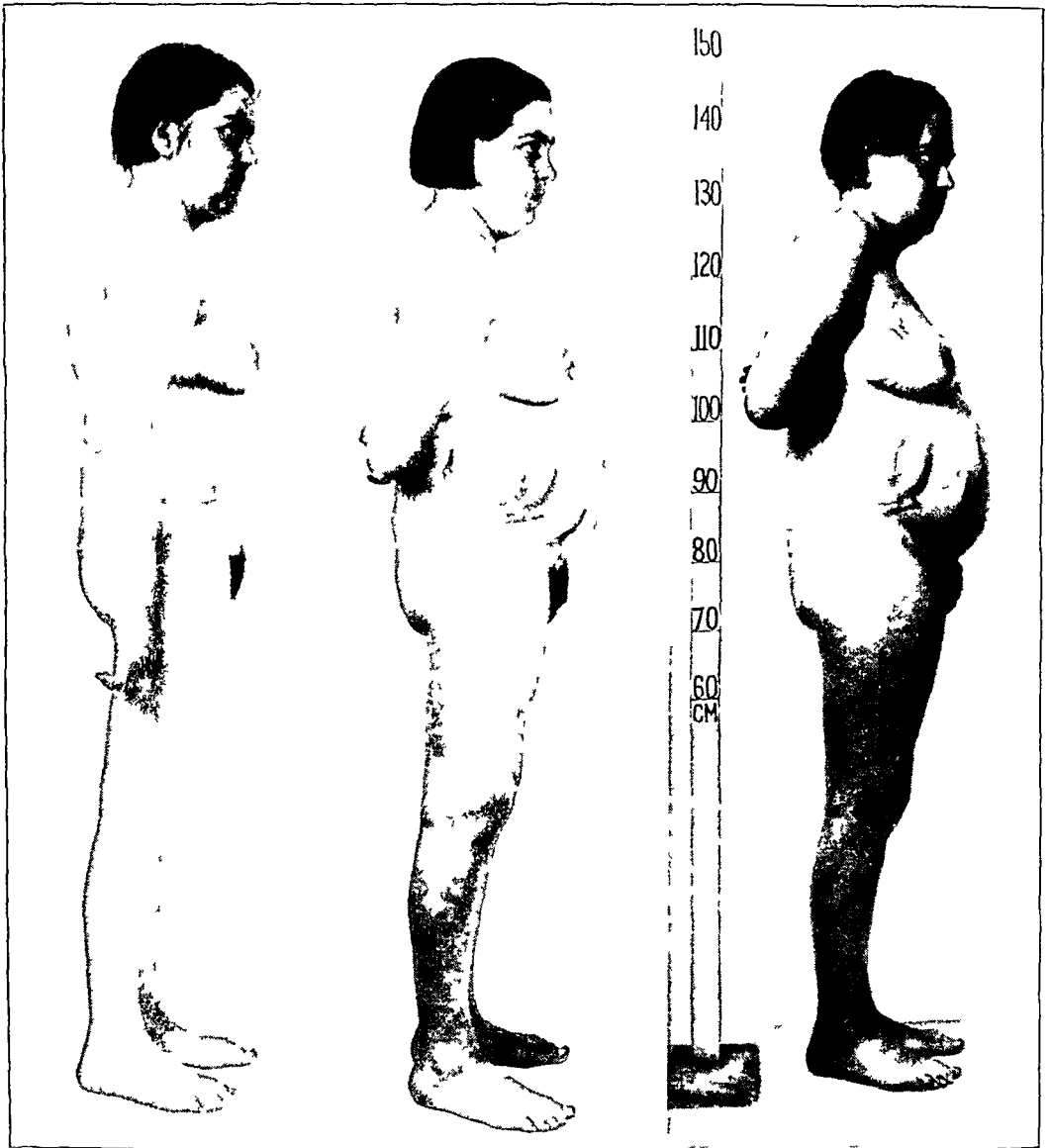
Her urine tested by two observers on both rabbits and immature mice proved to contain a follicular-stimulating substance indistinguishable in its effects from prolan A (rho I) \*

While from case to case, as is true of acromegaly, the syndrome varies considerably, its frequent association with a basophilic adenoma of the hypophysis must be something more than accidental The disorder proves

to be not uncommon, and suggestive clinical examples are found scattered in the literature dealing primarily with osteomalacia,<sup>89</sup> hypertension,<sup>92</sup> adiposity<sup>100</sup> and dermatologic topics,<sup>66</sup> or merely reported

\* In April, 1932, and again in June and August, she was given a series of deep x-ray treatments directed toward the pituitary body There was an early relief of backache In August, a definite diminution of the facial hirsutism was noted By September, her blood pressure, originally averaging 140/105, had dropped to 115/80 and has remained there In October, the abdominal striae began to lose their bright color In February, 1933, a normal menstrual period occurred after two years and ten months of amenorrhea with disappearance from the urine of the follicle-stimulating substance

as an instance of a remarkable disease<sup>107</sup> In a recent tabulation by Mr Henderson of the symptoms shown by the patients in our series with hypopituitarism due to chromophobe adenomas (verified or suspected), two of the patients were found to have an elevated blood pressure, and a review of their case histories makes it now obvious



April, 1932

July, 1932

October, 1932

Fig 14—Progress of acute pituitary basophilism (unverified) in six months period

that they were probably victims of basophilism. Indeed, an unmistakable case (that of Theresa L., cf fig 15) has come to light while reviewing, for the purposes of this paper the polyglandular changes found in the seventeen patients that died after operation for what was formerly diagnosed and indexed in the files as a chromophobe adenoma

Since hyperadrenalism and possibly other endocrine derangements may provoke a somewhat similar syndrome, it is unsafe as yet to pin too much faith on clinical symptoms alone, and only those examples of the disorder in which a postmortem examination has been held are dependable. Records are at hand of seventeen cases that came to autopsy,\* in fourteen of which the condition has been shown to be pituitary adenomas. In two of the three negative cases,<sup>137 90</sup> the



Fig 15—Miss L. Facial hirsutism with verified pituitary adenoma (? basophilic) invading cranial chamber

gland was said to have been normal without further specification, in the third, the Leyton-Turnbull-Bratton case<sup>83</sup> (in regard to which I over-reached myself in predicting<sup>37</sup> that a basophilic adenoma would be found), no lesion has been detected on recent serial sections

\* My attention has been called by Professor Gunther of Leipzig to another unmistakable case with a proved basophilic adenoma reported by Drs Theodor Bauer and Hans Wassing (*Zur Frage der Adipositas hypophysarea. Basophiles Adenom der Hypophyse*, *Wien klin Wchnschr* 26 1236-1243, 1913)



of the gland Of the fourteen cases actually associated with a pituitary adenoma, in three instances it was a large, unclassifiable growth, only fragments of which were examined, whereas in the other eleven it was a small, circumscribed typically basophilic lesion

For the purpose of showing the principal symptomatic and pathologic features of the fourteen cases with verified adenomas, the data,

*Verified Pituitary Adenomas Causing Syndrome of Basophilism,*

Case	Date of Report	Sex*	Age		Type of Adenoma Weight of Hypophysis	Principal Symptoms							
			Onset	Death		Abdominal Obesity	Amenorrhea	Hirsutism	Abdominal Striae	Glycosuria	Metabolic Rate (Basal)	Hypertension	Skeletal Decalcification
Schmorl <sup>111</sup> Molineus <sup>89</sup>	1913	♀	20	48	Large basophil	Yes	Yes	Yes +					Fracture
Anderson's <sup>8</sup>	1915	♀	21	26	Basophil	Yes	Yes	Yes	Yes			+185	Fractures
Reichmann's <sup>107</sup>	1919	♀	15?	36	"Eosinophilie"?	Face only	Yes	Yes				++210	Yes marked
Zondek's <sup>139</sup>	1923	♀	19	24	? Small	Yes	Yes	Yes	Yes +	Yes			Yes
Raab <sup>100</sup> Kraus <sup>70</sup>	1924	♂	?	31	Basophil 93 mg	Yes	Impotence	None	Yes ++	Yes			Yes
Parkes Weber's <sup>98</sup>	1926	♀	23	28	Basophil	Yes	Yes		Yes ++		+20	++230	
Bauer's <sup>14</sup>	1930	♀	34	36	Basophil	Yes	Yes	Yes ++	Yes	Yes	+28	+185	Suggestive x-ray
Wieth Pedersen's <sup>135</sup>	1931	♂	20	24	?	Yes	Impotence	None	Yes ++	Yes	Normal	+190	
Teel's <sup>120</sup>	1931	♀	15	20	Basophil	Yes	?	Yes			+33		
Moehlig's <sup>88</sup>	1932	♀	34	43	Basophil	Yes	Castrate	Yes	Yes		+31 -1	++230	
Bishop Close <sup>23</sup>	1932	♀	15	22	Basophil	Yes	Yes	Yes ++		Yes		++250	Fracture
Berblinger's <sup>22</sup>	1932	♀	?	?	Basophil	None	Castrate	Yes +	Yes				Yes
Miss L No 14327	1921	♀	18	45	Large invasive	Yes	Yes	Yes +	Yes	Yes	-4	+170	
Miss P No 42211	1932	♀	20	33	Basophil 71 mg	Face chiefly	Yes	Yes ++	Yes ++	Yes	-40 -1	++240	Fractures

\* ♀ indicates female ♂, male

so far as the fragmentary protocols which accompany many of the reports permit, have been assembled in the accompanying table \* To a detailed consideration of the last of these cases we may now turn As will be told, I had seen the patient briefly in consultation twelve

\* Attention may be drawn to the number of patients that died from acute pulmonary complications ascribed to edema

years ago and not again until she was recently referred to the hospital by Dr Goodale of Boston as having a case of probable pituitary basophilism

THE CASE OF MISS P *Onset of amenorrhea with plethoric adiposity purple striae atrophicae and hypertension at 19 years of age Relative subsidence of symptoms for ten years followed by exacerbation Multiple fractures, glycosuria and hyper-*

*with Principal Symptoms and Ductless-Gland Changes as Recorded*

Postmortem Findings								
Thyroid and Glands	Parathyroids	Thymus	Pancreas Islets	Hypertrophic Adrenal Cortex	Gonads	Arterio sclerosis	Osteomata	Cause of Death
Colloid goiter	Large adenoma?		Fatty		Atrophic		Brown tumors ++	?
Slightly enlarged	"Normal"	Atrophic		Yes	"Senile"	Yes	"Brittle bones"	Asthenia
Small, low cuboidal		Not identified	Normal	Yes 8.5-15 Gm	Atretic no corpora	Yes +	?	Following adrenalect
Small	?	Atrophic	Fatty		Follicular atresia		Yes ++	Erysipelas
Slightly enlarged	Large fatty 0.16 Gm		94 Gm	?	18.3 Gm, no spermatozoa		Yes ++	Sepsis
"Size walnut"		"Chiefly fat"		Yes 11.9 Gm	Atretic no corpora	Yes	?	Pulmonary edema
Small, low cuboidal			Normal	None	Follicular no corpora	Yes	?	Following adrenalect
Small			Normal	Yes				Respiratory dyspnea
Slightly enlarged		"Persistent"	Slightly enlarged	Yes	1 corpus luteum			Meningitis
Autopsy restricted to brain								Following thyroidect.
Low cuboidal					Atretic no corpora	Yes		Pulmonary edema
				Yes	Castrate		Yes "senile"	/
Small 11.5 Gm	Large fatty 0.1 Gm	Not identified	90 Gm fatty	Yes 9-10 Gm	Atretic no corpora	None (?)		Pituitary operation
Small 15 Gm	Large fatty	Atrophic	Fatty	Yes	Atretic no corpora	Yes ++	Yes slight	Pulmonary edema

*tension Death from acute pulmonary complications Postmortem examination Basophilic adenoma, hypertrophic adrenal glands, extreme atherosclerosis*

Oct 24, 1932 Admission of Miss P, 33 years of age

*Past History*—Born of healthy parents with an untainted family history, she, as a child, in addition to frequent "colds," had had measles, mumps, whooping cough, chickenpox and an attack of erysipelas, in 1908, an emergency appendectomy had been performed She attained a normal adolescence when 13 and grew

into an intelligent, vigorous and ambitious young woman. She entered college at 18, but became unhappy there and withdrew at the end of her second year. This determination she ascribes to restlessness, for she believes herself to have been "nervous, irritable, tense and emotionally unstable as long as she can remember." Because of her round face, she had been nicknamed "moony."

*Present Illness*—Her want of success at college may have been due to physical rather than temperamental causes. It at least coincided with the symptomatic onset of her malady, for in June, 1919, she ceased to menstruate, and subsequently while at a summer camp she developed a ravenous appetite. Always unduly fond of sweets, she began rapidly to gain weight, particularly noticeable in the face and abdomen. She became "gross, florid and bloated about the eyes (piggy-eyed)." During the summer she broke her ankle. Purplish striae of the body and arms began to appear at this time, and she has never since ventured to wear a sleeveless dress. In December, 1919, she found herself easily fatigued and acquired a definite polyuria and polydipsia. At the same time she began having headaches with blurred vision, tinnitus, dizziness and numbness of the hands.

Toward the end of February, 1920, because of a sudden fainting attack she came under the care of Dr. E. P. Joslin who found she had a moderate hyperglycemia with glycosuria and a basal metabolic rate of  $-30$  per cent. The puffy appearance of her eyes and face, dry skin, marked supraclavicular fat pads, and her complaint of being mentally sluggish strongly suggested myxedema.

On March 13, 1920, she was first briefly seen in consultation with Dr. Joslin. Her facial hypertrichosis and the peculiar disposition of the adiposity with extraordinarily widespread striae atrophicae associated with a moderate hypertension (140/100) indicated a polyglandular syndrome recognized as resembling that in the case of "Minnie G."<sup>38</sup> No therapeutic suggestions were made.

By January, 1921, she had become increasingly hirsute and "bloated," and at this juncture she came under the care of Dr. Timme at the Neurological Institute in New York. There she was given salt baths, graded exercises and various glandular preparations, including lutein, thyroid and pituitary. After four weeks' treatment, her weight was greatly reduced, the hirsuties had disappeared, and normal menstruation was resumed. From this time for a period of five years, she continued under various combinations of glandular treatment and regarded herself as reasonably well.

In 1926, her face again began to get heavily bearded and after trying various forms of proprietary treatment, she finally resorted to the daily use of a razor. In May, 1927, her adenoids, tonsils and impacted wisdom teeth were removed, and it was noted by the attendant that her blood pressure was high (155/115). In 1929, she had a "nervous breakdown." During March, 1930, she was elaborately studied at the Evans Memorial Hospital. At this time, the urine showed some albumin and occasional hyaline casts with normal phthalein test. She had a low sugar tolerance, a fluctuating hypertension, basal metabolic rate of  $-14$  per cent and a cardiac enlargement. The possibility of hyperthyroidism, virilism, primary ovarian disorder and myxedema was discussed. She was subsequently under observation at the Lahey Clinic as presenting a possible thyroid problem.

In January, 1931, the menstrual periods, after having been essentially regular for ten years, again ceased. In July, 1931, she was found to have a marked hypertension, from 220 to 250 systolic. She nevertheless passed the summer of this year with Grenfell in Labrador and enjoyed her work there.

In April, 1932, she fell and broke her humerus. During the following summer she became conscious of a change in disposition. She began to complain of polydipsia, occipital headaches, palpitation, shortness of breath, and swelling of feet and ankles. The fatness of face and shoulders, dryness and pigmentation of the skin

cyanosis of dependent hands and feet had markedly increased. She observed that large ecchymoses would follow the slightest bruise and that a cut or scratch would bleed excessively. At this juncture, in October, 1932, she was referred to the Brigham Hospital for study.

*Physical Examination*—The patient was a rather tall woman, 5 feet, 9½ inches (175.8 cm), weighing 63.5 Kg, with a peculiar moon-shaped, recently shaven face and clipped eyebrows. The eyes were puffy, there were posterior cervical and supraclavicular fat pads. She was not appreciably round shouldered other than

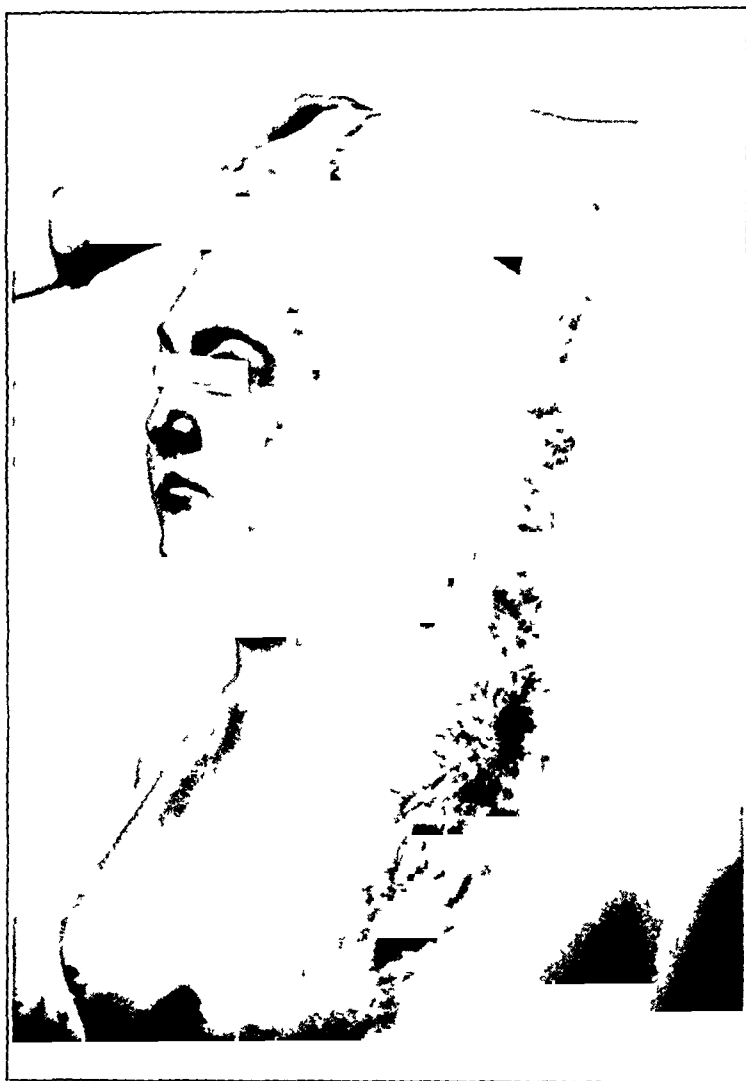


Fig. 16—Striae atrophicae of arm, axilla and breast

the cervical fat pad would account for. Though not particularly abdominous, the parietes were somewhat pendulous and flabby. The extremities did not participate in the adiposity. Over arms, axillae, breasts, abdomen, hips, groins and thighs were an extraordinary number of broad, pale striae atrophicae which deepened in color on slight rubbing (fig. 16). The lower extremities showed marked pigmentation and scarring of the dry and scaly skin with several large fading ecchymoses from recent trivial contusions.

The blood pressure averaged 220/170, the urine showed a trace of sugar and of albumin with no renal elements. There was a variable polyuria amounting to *circa* 3 liters. The basal metabolic rate was —10 per cent. The detailed blood exami-

nation showed 4,720,000 erythrocytes with hemoglobin (Sahli) of 106 per cent = 14.63 Gm. The nonprotein nitrogen was 46.97 mg per cent and the cholesterol 192.3 mg per cent, all other chemical tests being within normal limits.

Roentgenograms showed (Dr. M. C. Sosman) "a slight diffuse atrophy of the vertebral bodies without collapse or deformity, normal detail of the cranial bones, a sella of normal dimensions (fig. 17) but hazy outline. Multiple small tiny shadows in both flanks suggesting renal calculi—a common finding in hyperparathyroidism."

The patient was transferred to the Huntington Hospital where, through the kindness of Dr. J. C. Aub, her elimination was thoroughly studied. He reported essentially normal blood content for calcium, phosphorus and phosphatase and a

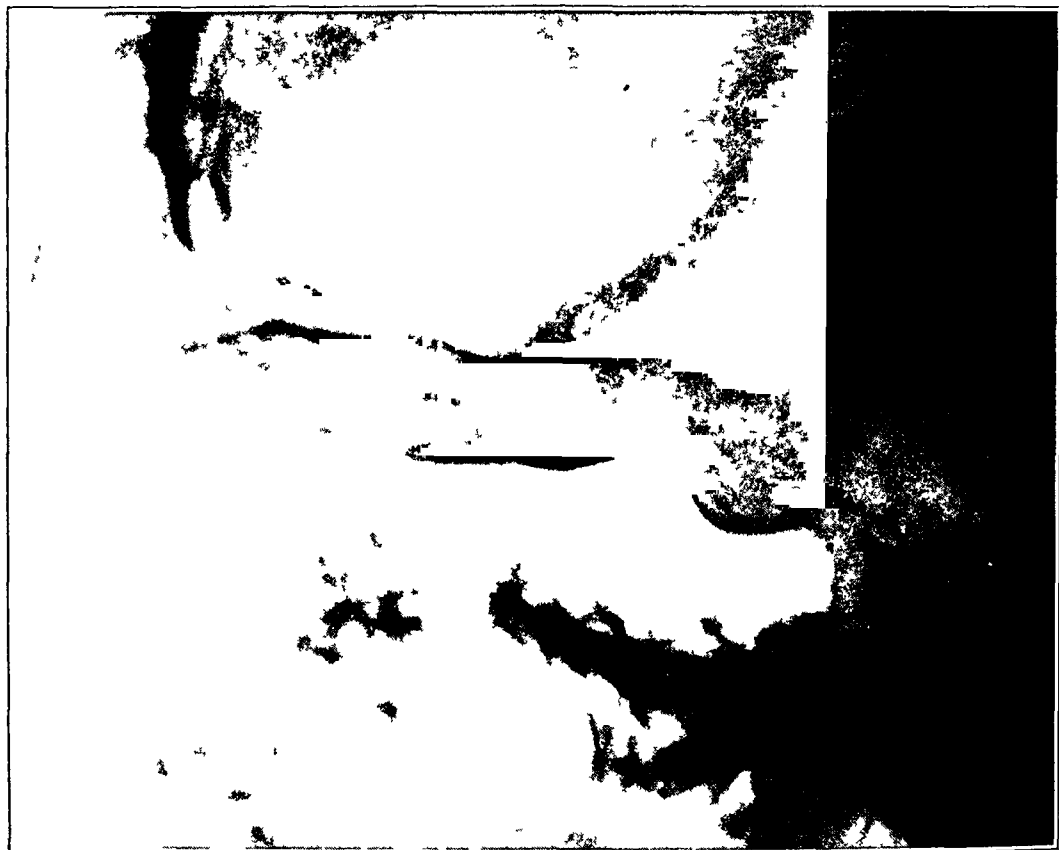


Fig. 17—Sella of normal configuration but hazy outline from decalcification in case of Miss P.

normal elimination of both calcium and phosphorus. She showed a low sugar tolerance and a high nitrogen output,\* as shown by an average loss of 6.7 Gm daily on a balanced diet containing 56 Gm of protein.†

\* This condition of "azoturia" (Woodyatt) was also observed in another example of the disease (case 11) in a former report.<sup>38</sup> In acromegaly, on the contrary, there appears to be a prompt utilization of nonprotein nitrogen.<sup>128</sup>

† Biologic tests of the patient's urine at this time were made by Dr. Fuller Albright who found on tests with rats no follicular-stimulating substance (rho I) such as had been found in the urine of Alice D. when tested on rabbits. This effect would normally be expected on the basis of Zondek's<sup>136</sup> explanation of amenorrhea as conditioned by the overproduction of the follicularizing hormone.

On her readmission to the Brigham Hospital, the pituitary body was irradiated on four successive days without immediate effects of any appreciable kind. She was discharged Nov 12, 1932. She returned to her home and resumed her usual activities. On the night of December 3, she had been to the theater, and though complaining of fatigue, she nevertheless joined a supper party and retired about midnight. An hour later, she awoke with dyspnea, became increasingly cyanosed, and died twelve hours later from what was supposed to be acute pulmonary edema.

*Autopsy* (Drs R Z Schulz, George Hass and author) —Forty-eight hours had elapsed before news of her death was received and an autopsy could be solicited and performed. The body had fortunately been well embalmed. The general condition, in brief, showed marked adiposity, particularly abdominal and mediastinal. There was no splachnomegaly or apparent anomaly of the liver (1,740 Gm), spleen

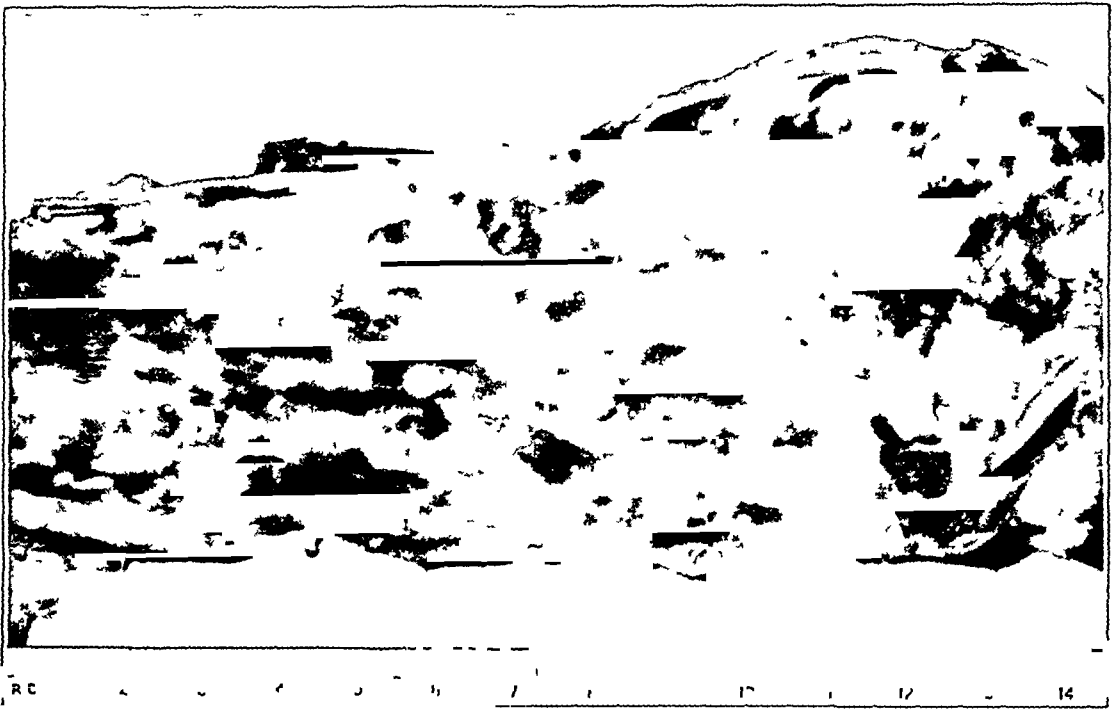


Fig 18—Marked atherosclerosis of aorta (natural size)

(100 Gm) or pancreas (65 Gm). The kidneys (170 and 175 Gm) had slightly adherent capsules, and on section numerous minute brownish calculi were visible in the calices of the pelves. The heart was enlarged (695 Gm), and the lungs (720 and 620 Gm) showed merely a few patches of congestion. There was an advanced degree of atherosclerosis chiefly apparent in the aorta and larger arteries. The bones, particularly the vertebral bodies, were easily cut with a knife, suggesting osteoporosis, but the tissue showed no gross change.

The histologic study of these organs and tissues principally showed (1) a chronic vascular nephritis, with sclerosed glomeruli and calcific deposits, (2) hypertrophy of the cardiac musculature, (3) apart from the arterial changes, an essentially normal structure of spleen, liver and pancreas, (4) an acute bronchitis and bronchopneumonia. The bones showed definite osteomalacia. The Paneth cells of the intestine were noted as being particularly prominent. A section of one of the cutaneous striae showed obliteration of the papillae of the corium with swollen and fragmented elastic fibrils. There was marked atheromatous degeneration of the aorta (fig 18) and large arteries.

*The Endocrine Organs*—The *adrenal glands* (fig 19) were hypertrophic, the left (14 Gm) measured 8 by 3 cm, the right (12 Gm) measured 7 by 4 cm and showed possible small adenomas on fresh section. A small nodule of adrenal tissue was identified in the stalk of the ovary. The heavy yellow cortical layer of each gland measured 2 mm in thickness. The evident hyperplasia was found histologically to be restricted to the zona fasciculata (cf fig 31) whose cells were distended with lipoid material.

No *thymic tissue* could be definitely identified in the mass of mediastinal fat, but an area of suspicious tissue was removed for study. Sections show only a few atrophic epithelial cords of thymic tissue, no Hassall's corpuscles being found.

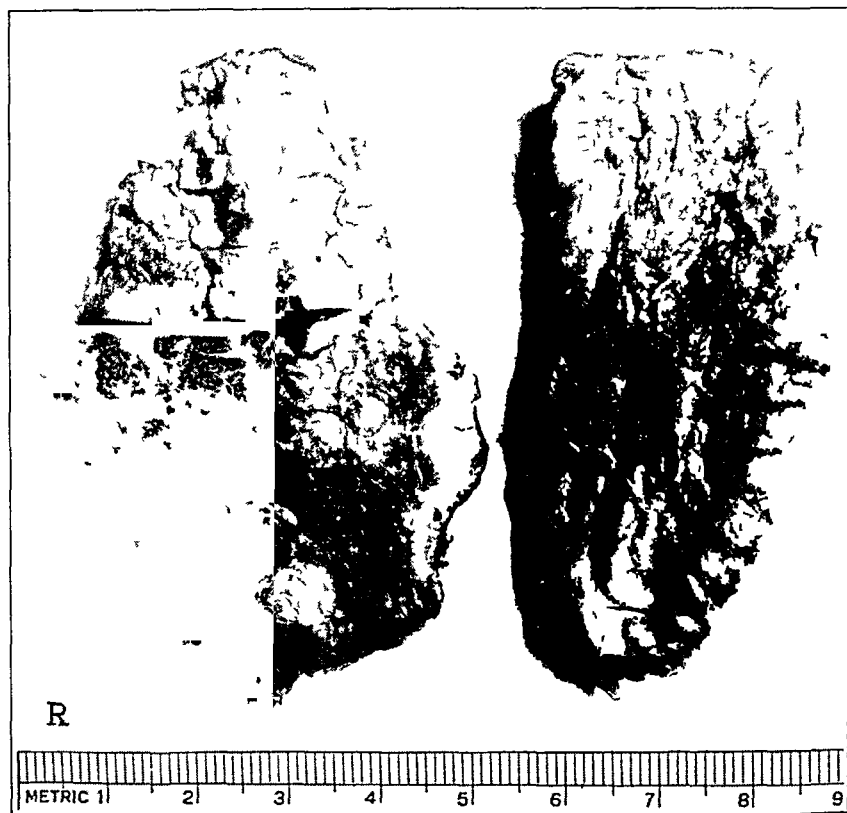


Fig 19—Cleanly dissected adrenal glands left, 14 Gm, right, 12 Gm (natural size) (Cf fig 31)

The *thyroid gland* (fig 20) was small (15.1 Gm). The parenchyma was composed of closely packed, rather small acini containing deeply-staining colloid. There were no papillary infoldings and the cells were of a low cuboidal type.

Four *parathyroid glandules* were identified, two of them slightly enlarged, measuring, respectively, 7 by 5 by 2 and 10 by 5 by 3 mm in diameter. Histologic study of the larger of them showed an essentially normal appearance apart from the fact that approximately two thirds of the volume of the gland was composed of fat. The cells are of the pale variety with a few scattered acidophilic elements and occasional droplets of colloid.

The *pancreatic islets* are numerous and appear to be normal in their structure.

The *uterus, tubes and ovaries* together (fig 21) weighed 65 Gm. The uterus was small, acutely retroflexed, and the endometrial as well as the cervical glands

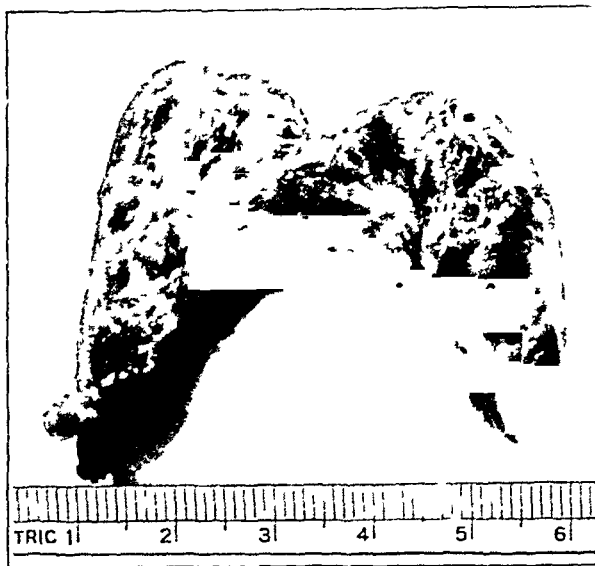


Fig 20—The 15 Gm thyroid gland (natural size) with adherent parathyroids



Fig 21—Uterus, tubes and ovaries (slightly reduced) , weight, 65 Gm



were found to be uniformly atrophic. The right ovary measured 40 by 25 by 20 mm and contained a superficially placed thin-walled cyst measuring approximately 25 mm in diameter. The left ovary measured 30 by 12 by 15 mm and showed no superficial cysts, but on fresh section numerous small cystic areas were apparent. Microscopically, the ovaries are found to have an essentially normal stroma in which a few large corpora albicantia and numerous follicular cysts of variable size are embedded (cf figs 33 and 34). The germinal epithelium is tall and columnar in type and does not appear to be abnormal, numerous primordial ova are to be seen. The cystic follicles are lined by atretic granulosa cells showing mitoses, in some of them a cumulus containing an atretic oocyte being discernible. The theca interna is well vascularized, cellular, both mitotic and pseudomitotic figures being numerous.

*The Pituitary Body*—Since it is with the hypophysis in this case that we are chiefly concerned, it deserves more detailed consideration. When the brain had been removed leaving the sella exposed, the diaphragma was found to be defective leaving exposed the larger portion of the upper surface of a nonprotruding hypophysis with its attached stalk. On carefully removing the gland (fig 22), it proved to be small (71 mg) and of normal appearance. Scarcely hoping to find the predicted lesion, the organ after fixation was serially cut in coronal sections.

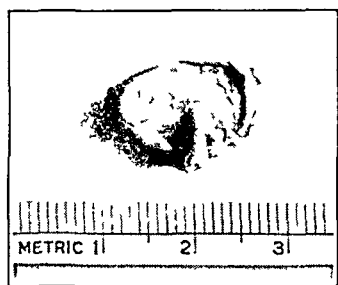


Fig 22—Upper surface of pituitary body (natural size), weight, 74 mg

Three of these sections are shown in low magnification in the accompanying photomicrographs (fig 23 A, B and C). The first of them (A) passes through the largest diameter of a lateral and anteriorly situated oval adenoma of pure basophilic type (cf figs 24 and 25) measuring 7 by 2.5 mm.

The second section (fig 23B) through the center of the gland transects the anterior part of the neurohypophysis and shows the marked invasion of the lobe by invading basophilic elements (cf fig 26). These invading cells, either by a holocrine or apocrine method of secretion, appear to disgorge their granular cytoplasm, masses of which are not only to be seen in the vicinity of the more deeply invading

cells (fig 27) but can be traced into the loose tissue of stalk and tuber from which region, however, the soluble substance has largely been dissolved out (?) in process of fixation of the tissues.

The third section (fig 23C) transects both neurohypophysis and stalk and shows (to the right side) a part of the anterior lobe in which acidophilic and basophilic elements are present in normal proportions. In this section only a small crescent of the highly vascularized tuberal cuff of the adenohypophysis remains apparent on the anterior (upper) surface of the transected stalk, whereas in figure 23B it completely surrounds the stalk. Due possibly to the patient's extreme cyanosis at the time of death, the "portal system" (Papa and Fielding,<sup>97</sup> Basir<sup>13</sup>) of diencephalo-hypophysial veins which passed through the stalk was greatly engorged (fig 28). On high power magnification, some of the communicating vessels of this system prove to be filled, almost to the exclusion of erythrocytes, with what appears to be granular secretion (fig 29). Clumps of the same appearing substance are to be seen here and there in the loose meshed glia of the neurohypophysis and can be traced even into the stalk and region of the tuberal nuclei.

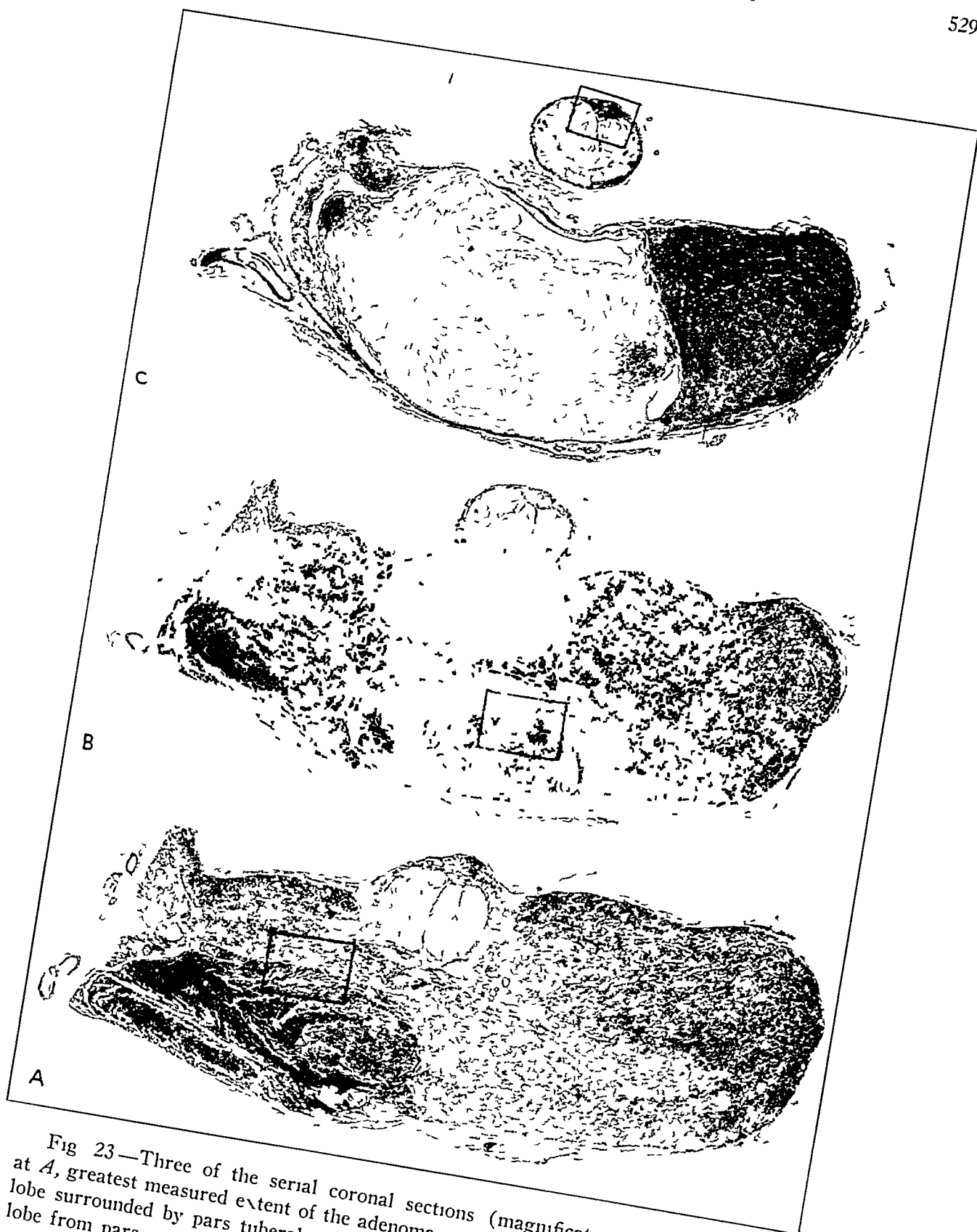


Fig 23—Three of the serial coronal sections (magnification  $\times 7$ ) showing at A, greatest measured extent of the adenoma and the anterior margin of posterior lobe surrounded by pars tuberalis, at B, extensive basophilic invasion of posterior lobe from pars intermedia, at C, transsection of stalk as well as of posterior lobe, small areas of basophilic invasion being still evident at its lateral aspects

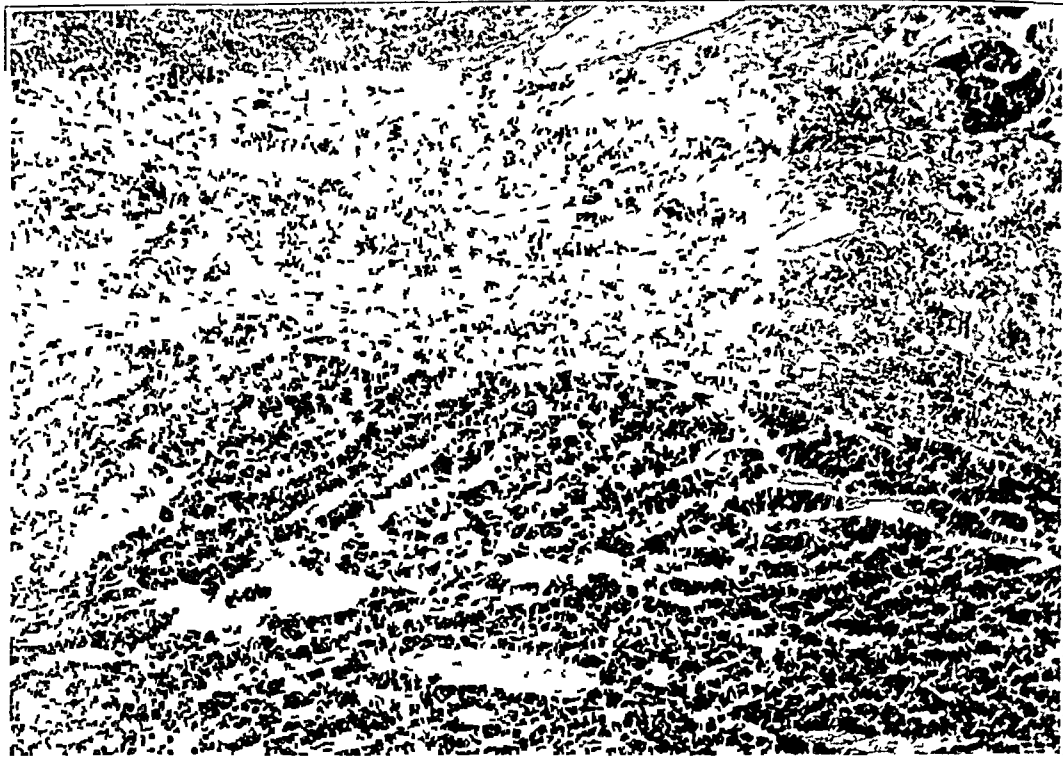


Fig 24—Margin of basophilic adenoma (magnification  $\times 70$ ) from squared area in figure 23 *A* Note small isolated collection of basophils in upper right corner, such as occur in other parts of the lobe

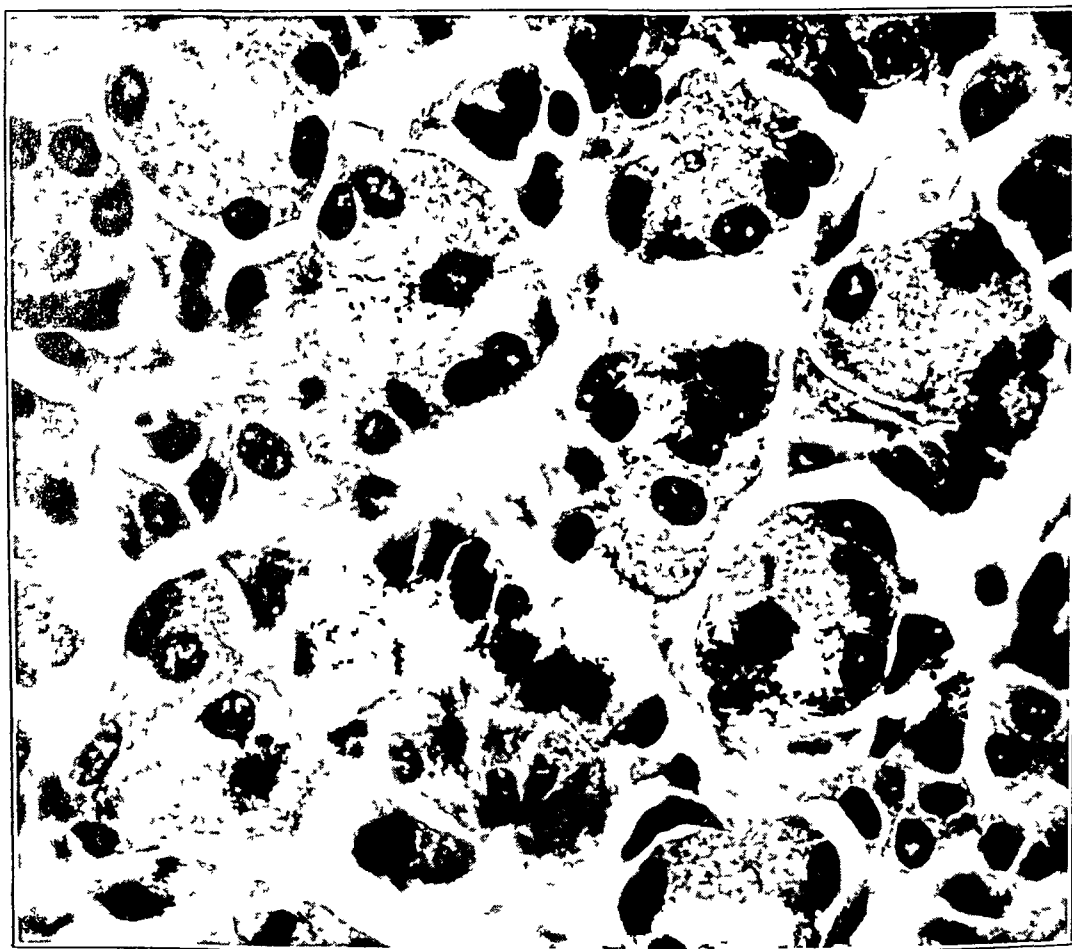


Fig 25—Large basophilic elements composing tumor with typical vacuolated cytoplasm (magnification  $\times 850$ )

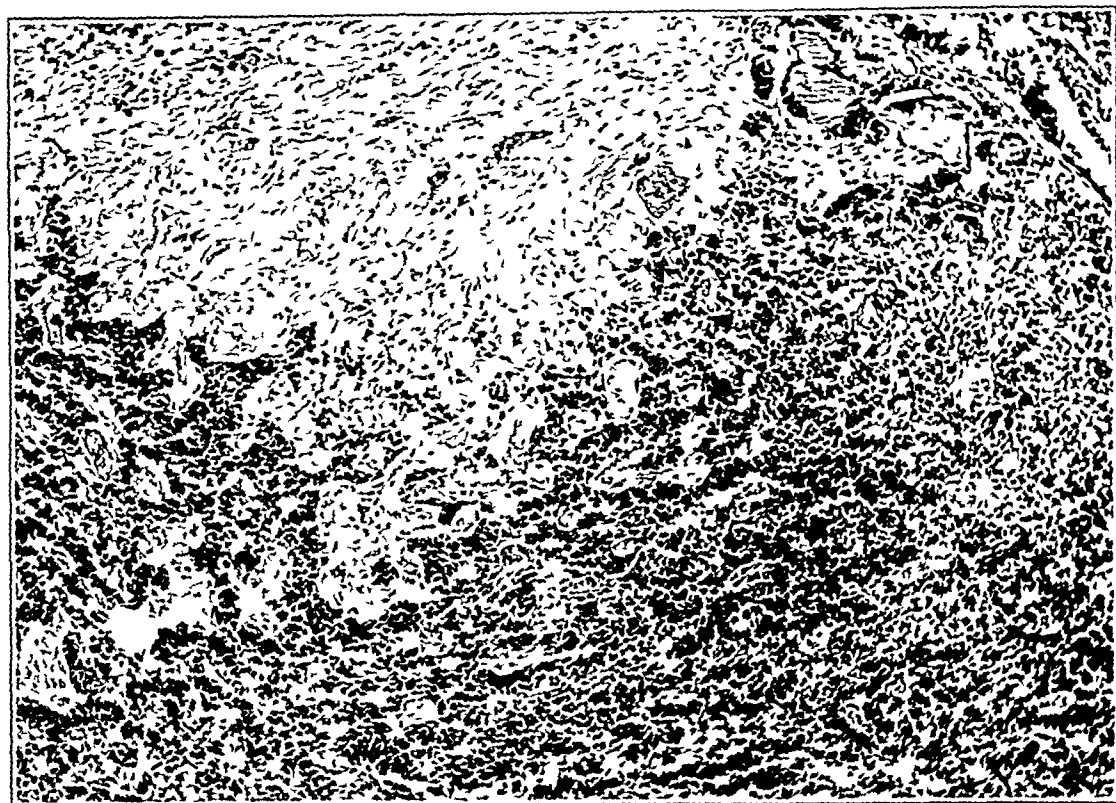


Fig 26—Squared area in figure 23 *B* (magnification  $\times 70$ ) showing invasion of the posterior lobe by cords of basophil cells from pars intermedia

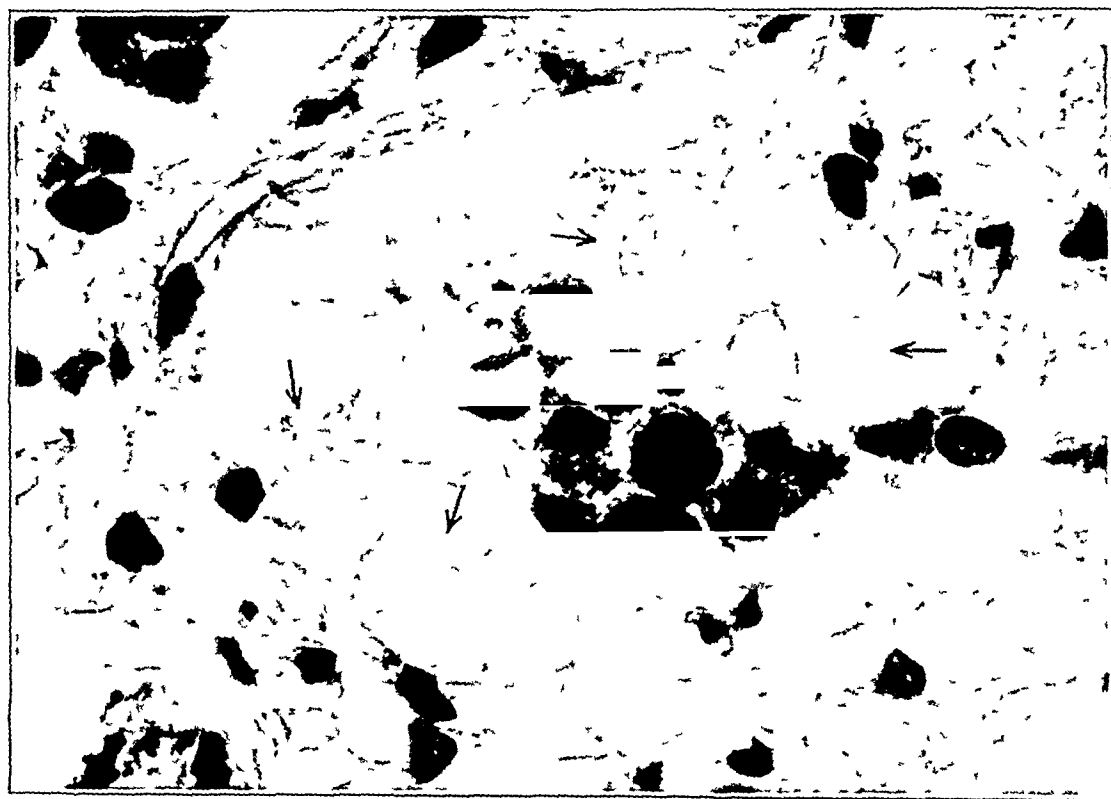


Fig 27—Disorgement of ripened cytoplasm (arrows) of invading basophilic elements into loose tissue spaces of posterior lobe (apocrine secretion), the ghosts of nuclei still apparent in many of the granular masses



Fig 28—Posterior edge of pituitary stalk (cf squared area in figure 23 C), the bundle of dilated “portal” veins passing from pars distalis through pars tuberalis to hypothalamic (chiefly tuberal) nuclei (magnification  $\times 100$ )

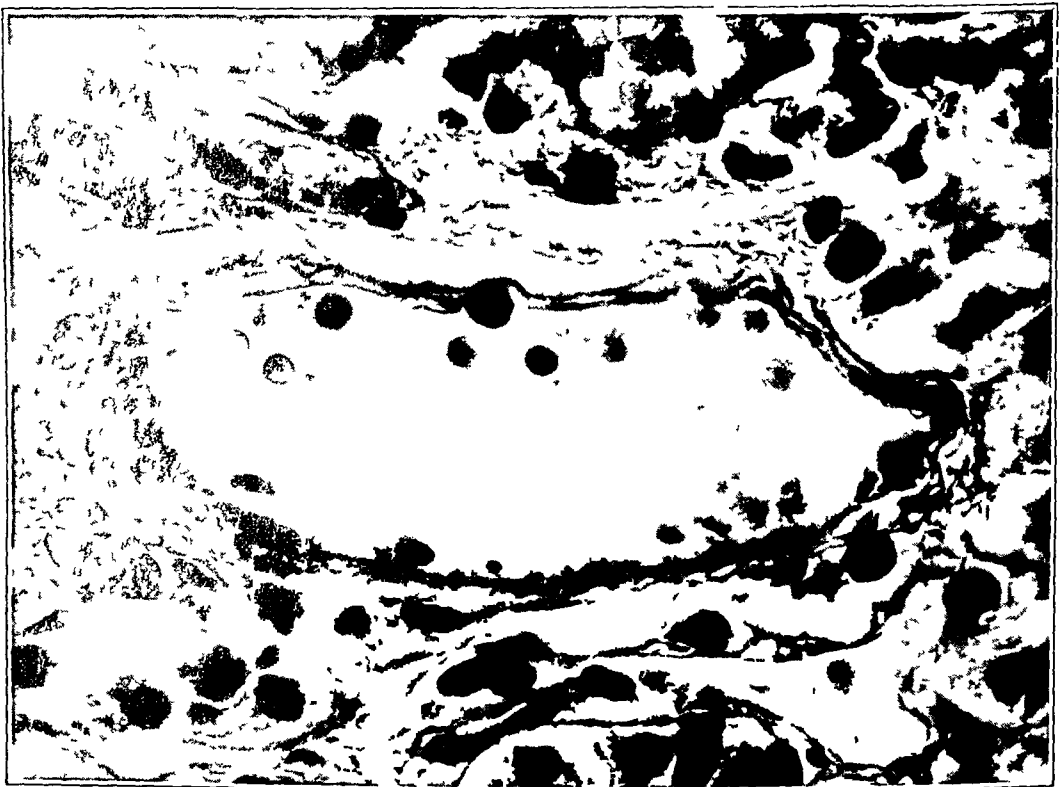


Fig 29—A “portal” vein in pituitary stalk so packed with the finely granular secretory product (?) as almost to exclude red blood corpuscles (magnification  $\times 850$ )

How can one account for the symptomatic effect of this peculiar lesion? That it is an adenoma composed purely of basophilic elements is beyond question. But does it operate merely by pouring its specific hormone into the general circulation, or does the excess of basophilic elements that congregate around the pars intermedia and infiltrate the infundibular lobe indicate the participation of the neurohypophysis in the symptom complex? And if so, does the character of the posterior lobe secretion become modified under these circumstances or merely increased?

The attempt to answer these questions obliges us to consider (1) the secondary effects of the "basophilic" hormone, whatever it may be, on the other organs of internal secretion, and (2) the possibility that the posterior lobe has been activated by the lesion. To this possibility we may first turn.

#### 1 BASOPHILIC ACTIVATION OF THE NEUROHYPOPHYSIS

A more or less protuse infiltration of the posterior lobe by viable, normally staining basophilic elements from the pars intermedia has been often described, attention having been first called to it by Thom<sup>130</sup> (1901) who believed it to be a peculiarity of advancing age. It was noted by Erdheim<sup>17</sup> (1903) also as a characteristic of old persons, by Lowenstein<sup>85</sup> (1907) as a feature of the pituitary adenomas, by Herring<sup>67</sup> (1908) who found that thyroidectomy increased the cellular invasion, by Lucien<sup>86</sup> (1909) who distinguished the cells as basophilic elements and believed the invasion to be more pronounced in chronic maladies of the aged. It has also been discussed from various aspects by Tolken<sup>132</sup> (1912), by Plaut<sup>96</sup> (1922), and by Lewis and Lee<sup>82</sup> (1927), by Kraus and Traube<sup>76</sup> (1928), by Berblinger<sup>19</sup> (1927) and most recently by Zondek<sup>137</sup> (1933) and by Guizzetti<sup>62</sup> (1933).

With all this accumulative histologic evidence of the frequency of the process, little has been said of its functional significance or of its relation to an associated clinical syndrome. It was once reported as a distinguishing feature of the gland in an early case of acromegaly<sup>41</sup>. However, in no instance has the process been so striking as in the neurohypophysis of this patient, nor have I ever observed before the masses of hyalinoid secretion in the portal vessels of the stalk which are now known to terminate in a plexus surrounding the tuberal nuclei.\*

The basophilic elements, consequently, as suggested by the conditions found in the serially sectioned gland of Miss P, may not only exercise their effects through the blood stream, but their product, possibly modified during its passage through the posterior lobe and stalk, may exercise a local effect, presumably stimulatory, on the diencephalic nuclei in whose neighborhood these veins appear to disgorge their product.

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\* The few sections I have of the Raab-Kraus tumor (cf fig 22, case 10<sup>38</sup>) show also a heavy invasion of basophils apart from the tumor mass which appears to have arisen in the pars intermedia. Professor Kraus mentions this in his protocol<sup>76</sup>.

There is nothing revolutionary in this idea. Herring's conception<sup>67</sup> (1908) of an infundibular pathway for the secretion of the pars intermedia was independently advanced by Thaon<sup>129</sup> (1907), by Livon<sup>84</sup> (1908), by Cushing and Goetsch<sup>41</sup> (1910), and by Edinger<sup>44</sup> (1911) and was warmly supported by Remy Collin<sup>27</sup> (1928) in his monograph, 'La neurocrinie hypophysaire.' While these observations were for the most part based on the anatomic study of the tissues, it has recently been shown (1933) by Zondek and Krohn<sup>138</sup> in a series of striking experiments that the pars intermedia elaborates a pigmentary hormone, intermedin, which by a novel and delicate test can be traced through stalk, tuber, and into the fluid of the third ventricle. How many more of the several posterior lobe principles will be found to be similarly distributed remains to be seen.

To such a neurotropic effect, for want of a better explanation, may be ascribed the adiposity, the hypertension and the late vascular changes, which may now be briefly taken up one by one. While it is possible that the glycosurias that occur in these states of basophilism also belong in this same category, their separate consideration will be postponed to a later section dealing with the pancreatic islets. While much that follows is speculative, and based on the examination of this single case it will at the same time prove, I hope, to be provocative of further study as new opportunities arise.

*The Adiposity*—The rapid onset of an obesity which spares the extremities and is chiefly abdominal, while it was not pronounced in this particular patient, has nevertheless been a striking feature in all but one or two of the reported examples of pituitary basophilism (cf table of cases). We have learned both from animal experimentation and clinical experience that a moderate degree of adiposity is a feature of pituitary insufficiency, but as Smith has so clearly shown in the rat<sup>110</sup> states of extreme obesity comparable to that under consideration can be experimentally produced only by a tuberal injury.

To a presumed injury of the tuber from pressure against the dorsum sellae, Raab<sup>100</sup> ascribed the rapidly acquired obesity of his patient. While this might be mechanically possible with a large tumor, the explanation could scarcely apply to an unenlarged gland. The effect nevertheless may conceivably be a tuberal one but for quite a different reason—namely on the basis of a tuberohypophysial mechanism hyperactivated by secretory products from the pars intermedia. And the fact that many of the patients with pituitary basophilism show varying degrees of polyuria and polydipsia is not unfavorable to this interpretation.

*The Hypertension*—Whatever may prove to be the cause of the acute adiposity, the attribution of the hypertension, which characterizes the clinical syndrome in all cases, to an excess of neurohypophysial secretion has much in its favor. Compatible with this view is the fact that patients with chromophobe adenomas, which serve to flatten the posterior lobe out of all recognition invariably have a subnormal blood pressure. Heretofore the vascular hypertension of polyglandular dis-

orders has been ascribed to an adrenal source, but the hyperplasia solely affects the cortex of these glands and the neural core of chromaffin cells which elaborate epinephrine remains so far as can be told histologically unaltered

The long recognized pharmacodynamic properties of posterior lobe extracts and their relation to the utilization and elimination of water, fat and carbohydrates have only in recent years begun to be interpreted in terms of clinical experience. Hofbauer,<sup>69</sup> in 1918, in view of the pressor and antidiuretic effects of the extract together with the known enlargement of the hypophysis during gestation, suggested that the pregnancy toxemias, especially eclampsia, might be due to overaction of the posterior lobe. This view has received experimental support by numerous workers, culminating in the demonstration by Anselmino and his collaborators (references 4, 5 and 70) not only of an antidiuretic substance in the blood of all cases of nephropathy and eclampsia, but of a pressor substance as well when the disorders are accompanied by high blood pressure. Naturally, the substance was looked on as a product of the posterior lobe, which we may take to mean primarily of the pars intermedia.

For many years certain Continental pathologists have given painstaking attention to the cytologic changes in the adenohypophysis in various diseases. Berblinger<sup>18</sup> was the first to call attention to the increase of the basophilic elements of the gland in advanced renal disease, more particularly noticeable in uremia<sup>20</sup>, and Kraus and Traube<sup>80</sup> have amplified this to include hypertension and a confusing variety of other disorders. So far as I can determine however, neither they nor others<sup>68</sup> who have confirmed their observations have emphasized the significance of the basophilic invasion and resultant activation of the neurohypophysis.

*Cholesteremia and Atherosclerosis*—Coincident with the acute adiposity, most of the patients with basophilic adenomas, in whom the determination has been made, have shown a moderate cholesteremia. This Kraus<sup>78</sup> looks on as the primary factor, the increase of lipoids in the adrenal cortex being secondary, causing in turn the multiplication of the basophilic cells in the pituitary body. However this may be—and it seems an improbable sequence—there can be little doubt of the damaging effect of the cholesteremia on the blood vessels. A deposition of cholesterol esters in the intima Ashoff looks on<sup>9</sup> as the starting point of atherosclerosis, while the appearance of calcium in the media is a secondary process which appears to be accelerated by active ergosterol produced by irradiation of body lipoids.

The combination of cholesteremia therefore, with the increase of blood calcium which accompanies the osteomalacia would seem to be a combination most favorable to the production of the vascular disease seen in these states of pituitary basophilism: the mild degree of nephritis

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\* Attention should be drawn to the fact that for their tests Anselmino and Hoffmann utilized the rabbit—a notoriously unreliable experimental animal.



being a secondary effect. And it is quite probable that even should the cholesteremia, as in this particular patient, not have been apparent in the later stages of her disease, the stiffening of the vessels which had taken place would in themselves have served to perpetuate her hypertension. In one or two other examples of the disease, a notable fall of blood pressure has coincided with a temporary subsidence of all other symptoms.

## 2 SECONDARY ENDOCRINE EFFECTS

Should the basophilic cells prove to be responsible for the gonadotropic hormone, the syndrome produced by an adenoma of these elements is scarcely what one would expect. So far as I am aware, however, the gonadotropic hormone from the pituitary body, like that from other sources, has been employed only for short time sex-maturing observations (cf. the early adolescence of Alice D., p. 516, and of Teel's case<sup>126</sup>), and no one has set out to learn what might be the systemic effects of its continued administration over long periods. While this will undoubtedly come to be done, let us see what interpretation in terms of the experimental laboratory can be offered in the present state of our knowledge for such effects of the three pituitary adenomas as may conceivably be ascribed to functional disturbances of subsidiary glands.

A primary adenoma of any ductless gland doubtless affects by its excessive secretion the secretory activity of all others, just as does the extirpation or pathologic destruction of any one member of the series. But a hypersecretory adenoma or a destructive process in no other gland produces such grossly evident secondary changes in the series as occur when the disorder primarily affects the pituitary body. On this fact the pathologic and experimental evidence of its dominance chiefly rests. What effect primary lesions of the subsidiary endocrine organs actually have on other members of the series is usually shown most strikingly as a reciprocal response on the part of the adenohypophysis itself, e. g., the increase of elements of certain types after thyroidectomy, adrenalectomy and castration.

Unfortunately, we have only fragmentary data regarding the gross and microscopic changes of each subsidiary organ consequent on the experimental withdrawal or increase of the two principal hypophysial hormones separately, chief attention having been paid to the gonads, the thyroid and the adrenal. The sensitivity of the gonads is well known, but the adrenal cortex and thyroid are scarcely less sensitive, as has been amply shown both in the dog and rat. A prompt shrinkage of these structures follows hypophysial extirpation, and a no less prompt hyperplasia follows the injection of prepared extracts of the growth hormone.

Clinicopathologic experience, so far as it goes, coincides with these observations. A chromophobe adenoma whose effects, as we have seen

are comparable to a more or less complete hypophysectomy, is followed by atrophy of adrenal cortex, of thyroid and of reproductive apparatus. On the other hand, acromegaly, the clinical expression of experimental overgrowth, is associated with a notable hyperplasia of these organs, as has elsewhere been emphasized<sup>40</sup>

Before entering on a more detailed discussion of these matters, it may be convenient to have before us a diagram (fig 30), which indicates (roughly, to be sure, for want of a sufficient number of detailed weights and measurements) what gross changes the acidophilic adenomas of acromegaly, what the basophilic adenomas of the disorder

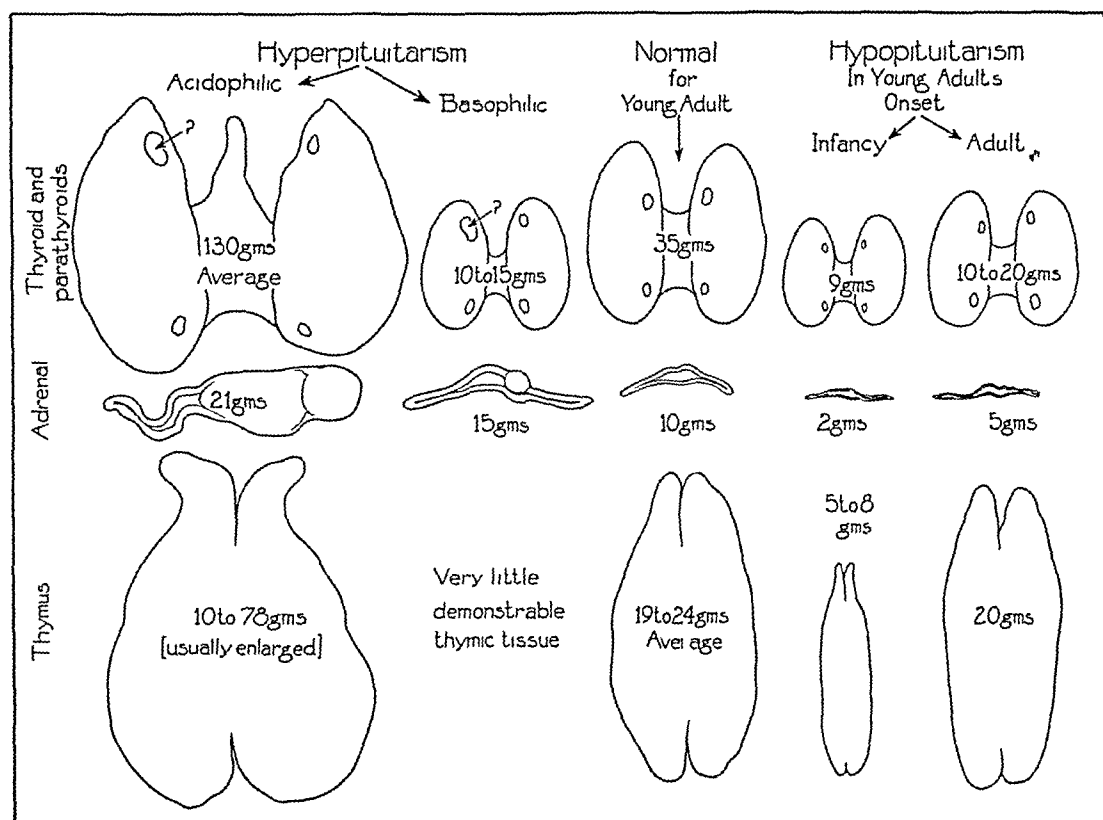


Fig 30—A rough diagram (capable of improvement with further data) to indicate, for comparison with the normal organs of the young adult, the secondary changes in the ductless gland series consequent on hyperpituitarism, both acidophilic and basophilic, and on hypopituitarism of young adults which has started (1) in infancy and (2) in adult life (Reduced two-thirds from natural size)

under consideration, and what the dual hypopituitarism of chromophobe adenomas tend to bring about. Not enough is known of the interstitial cells of the gonads to represent them in the schema, nor are sufficiently definite changes observable in the pancreatic islets to justify their inclusion.

*Symptoms Referable to the Thyroid*—In these states of pituitary basophilism, the thyroid appears to be surprisingly inactive. In the case

under discussion, the gland was small and the basal metabolic rate low on the several occasions when it was tested\*. This corresponds to the condition of the gland in hypopituitary states, whether clinical or experimental.

In clinical acromegaly, on the other hand, the gland becomes progressively, sometimes enormously enlarged, and many acromegalics show an elevated metabolism. This may at times be so high that the enlarged thyroid has often been operated on for assumed primary hyperthyroidism. And while this activation of the thyroid with accompanying increase of metabolic rate is usually interpreted in terms of the adenohypophysis, it must not be overlooked that posterior lobe extract and its derivatives, pitressin and pitocin, have been shown by Geiling and his co-workers<sup>59, 61</sup> to have, both in man and dogs, a marked effect on gaseous metabolism.

To experimental alterations of pituitary function, the thyroid, as is well known, responds promptly. Its rapid disorganization and subsequent atrophy, though wrongly interpreted, was observed in our early canine experiments. On the other hand, in experimental gigantism in the rat and dog, the gland becomes quickly hypertrophic. It is now claimed, indeed, by Junkmann and Schoeller<sup>73, 74</sup> that the gland elaborates a separable thyrotropic hormone, and Evans believes that convincing proof of this lies in the fact that a thyroid-stimulating property remains in the extractives after removal by precipitation of both the growth-promoting and the sex-maturing fractions.

*Parathyroid Participation*—The clinical evidences of skeletal decalcification were less marked in the case of Miss P. than in many other recorded examples of the disorder. There was a history of two or three fractures without severe trauma; the roentgenologic appearance of the bones during life betrayed the mild degree of osteomalacia that was found after death, and the multiple renal calculi were characteristic of hyperparathyroidism. On the other hand, she never became round shouldered from collapse of the vertebral bodies, and no increase of calcium elimination was demonstrable at the stage of the disease when her mineral metabolism was under investigation. The glandules were found to be grossly enlarged, but this proved to be due to an interlobular infiltration with fat.

Far more is known about the internal secretion of the parathyroids and its effects than of the cells which produce it. Parathormone, in the opinion of Collip's co-workers,<sup>131</sup> activates the osteoclasts with consequent loss from the skeleton of its calcium phosphate, the kidneys in time becoming affected in their efforts to unload from the blood its excess of mineral salts. In hyperparathyroidism associated with adenomas of the glandules, a wholly similar process occurs, a high blood

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\* The reading (cf. table of cases) was said to be high in cases 3, 4, 8 and 9, but this in no instance was shown to be associated with any demonstrable hyperplasia in the thyroid when it came to be examined post mortem.

calcium with a low blood phosphorus and increase of phosphatase having been shown by J. C. Aub and his co-workers<sup>2, 15</sup> to be a uniformly characteristic feature of the malady. But whether in the absence of an adenoma a physiologic activation of the glandules may cause corresponding though milder effects remains conjectural for want of precise information (such as we have for the thyroid gland) regarding the histologic changes in the glandules which are an expression of functional hyperplasia.

Since no definite inter-relationship with other glands of internal secretion has heretofore been established for the parathyroids, it is venturesome on symptomatic grounds alone to suggest that we have clinical evidence of it here. With one possible exception, no abnormalities of any kind have been observed in the parathyroid bodies of persons who have succumbed to pituitary basophilism. The exception was a case reported twenty years ago, first briefly by Schmorl,<sup>111</sup> and subsequently more in detail by Molineus<sup>89</sup> together with two other examples of advanced osteitis deformans, in both of which a parathyroid adenoma was found. Naturally enough, therefore, the osteomalacia in the third case was likewise ascribed to hyperparathyroidism on the basis of an oxyphilic hyperplasia without adenomatous formation. Clinically, this case, as reported, had all the hallmarks of the malady under discussion. The large basophilic adenoma which was found post mortem was looked on as an incidental lesion playing no part in the syndrome.

Osteomalacia, indeed, has often been so striking a feature of the post-mortem findings in pituitary basophilism that the protocol of the autopsy has been largely given over to it. Nevertheless, it is rare for the process to be so marked that it could be mistaken for von Recklinghausen's generalized osteitis fibrosa. It may be that this advanced type of decalcification may require an amount of parathormone quite beyond the capacity of a simple hyperplasia and only be delivered by a functionally active parathyroid adenoma.

Unfortunately, the parathyroid glandules have not always been looked for and examined, but when this has been done an unmistakable adenoma has never been detected. And apart from the multiple skeletal lesions in the Molineus case, the only instance of a possible "brown tumor" occurring in a patient with pituitary basophilism was the pelvic lesion roentgenologically picked up in the case of Alice D., to which brief allusion has just been made (p. 516).

*The Thymus*—A thorough dissection of the mass of mediastinal fat in this patient failed to detect any isolated organ, and only shreds suggestive of thymic tissue were microscopically demonstrable. Similarly, in all other cases of basophilism that came to autopsy the gland has been reported as small whenever specific reference has been made to it. To this, however, there is one notable exception, namely, the case

with many of the clinical features of pituitary basophilism reported by Leyton, Turnbull and Bratton<sup>83</sup> in which a cancer of the thymus was found in the absence of any pituitary abnormality.

On the other hand, the thymus may be greatly enlarged in association, curiously enough, both with chromophobe and with acidophilic adenomas. In what was probably the first case of acromegaly ever thoroughly examined post mortem, Fritzsche and Klebs<sup>55</sup> found the thymus to be so markedly hypertrophic they were inclined to ascribe the disease to this source rather than to the less strikingly large pituitary body. Just what these hyperplastic revivals of the dormant structure signify, the Sphinx among the glands of internal secretions (if it actually is one of them) has not yet revealed.\*

*Pancreatic Islets* VERSUS *Hypophysis* in *Sugar Metabolism*—The patient, as will be recalled, came under Dr. Joslin's care because of her glycosuria, a symptom which has been even more marked in other examples of the disorder. In one instance (case 11 of an earlier report<sup>38</sup>) during an acute exacerbation of the malady the hyperglycemia was found to be uncontrollable by insulin. Since then, however, the glycosuria of that patient has spontaneously subsided, and as the adiposity and hypertension have also grown less, he, at the present time, in spite of the residual stigmas of the disease, enjoys reasonably good health.

Similar waves of hyperglycemia, as is well known, characterize acromegaly. In this disorder also, not only is the glycosuria difficult to control by insulin, but it may sometimes spontaneously disappear when hypopituitary symptoms ultimately come to be superimposed on the original clinical picture. In view of all this, doubts naturally arise regarding the rôle of the pancreatic islets in pituitary (acidophilic or basophilic) diabetes, for what is known as primary pancreatic diabetes shows no remissions of this sort.

Allusion has already been made (p. 489) to the peculiar state called cachexia hypophyseopriva which we observed as a sequel of our early canine hypophysectomies and which usually proved fatal. While we did not then know enough about carbohydrate metabolism to realize that this might represent a state of acute sugar deprivation (now known as hypoglycemic shock), we did soon learn that a greatly increased tolerance for carbohydrates would be shown by the animals that recovered from the operation. And we soon learned, too, that a corresponding high tolerance for sugars was characteristic of clinical hypopituitarism. It was already known that posterior lobe extracts caused glycosuria in certain animals, and we were therefore misled into ascribing the disturbances of sugar metabolism solely

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\* What may be the relation, if any, of the fat organ of batrachians and of hibernating mammals to the thymus I am not enough of a comparative zoologist to know. It will be recalled that in the Smiths' early report<sup>119</sup> on the responses of the tadpole to hypophysectomy, the thyroid, parathyroid and adrenals failed to develop, but the fat organ remained hypertrophic, injections of posterior lobe extract caused it to disappear (cf. Rasmussen<sup>102</sup>).

to this part of the gland\* Hence, after working over the problem at length, it was stated<sup>60</sup> that "If loss or diminution of the internal secretion of the pancreas robs the tissues of their power of metabolizing carbohydrates, certainly loss or diminution of the hypophyseal posterior lobe greatly enhances their power in this respect" So marked was the degree of tolerance for sugar, we had come to believe that a preliminary hypophysectomy might actually counteract the fatal effects of removing the pancreas, but we never got so far as to put this to the supreme test of a total pancreatectomy

It meanwhile had been observed by Aschner<sup>8</sup> that after a transphenoidal hypophysectomy glycosuria could be easily produced by a piqûre of the tuber And this was also found to be true in the course of our later efforts<sup>134</sup> to work out the autonomic control of the gland by tracing the pathway of neuroglycosuric discharges That the tuberal nuclei directly controlled the neurohypophysis was then not even surmised

New light was thrown on the question favorable to posterior lobe participation in carbohydrate metabolism, when Buin<sup>26</sup> (1923) discovered the antagonistic effect of insulin and neurohypophyseal extracts, the latter serving to counteract the symptoms of hypoglycemia Others promptly corroborated this observation, and it was soon found by Houssay and Magenta<sup>72</sup> (1924) that hypophysectomized dogs are hypersensitive to injections of insulin, and the same now proves to be true of hypophysectomized monkeys<sup>64</sup> and also of patients with a marked hypopituitary syndrome

This was further amplified in an important paper (1927) by Geiling and others,<sup>57</sup> who showed not only that removal of the canine anterior lobe alone, leaving the posterior lobe intact, failed to cause insulin hypersensitization, but also that the hypoglycemic "shock" so easily produced by giving insulin to totally hypophysectomized dogs can be prevented by the coincidental injection of posterior lobe extract Finally, Cowley<sup>30</sup> has recently (1931) demonstrated the presence in the blood of hypophysectomized dogs of a substance having a marked hypoglycemic action All things considered, therefore, evidence abounds that the high tolerance for carbohydrates in hypopituitary states is due to an increase of the insulin content of the blood due to the withdrawal of the counteractive posterior lobe principle

So much, then, in behalf of the neurohypophysis What now can be said of the adenohypophysis in relation to sugar metabolism?

While it was observed that some of our laboratory dogs, in process of becoming acromegalized by injection of Evans' growth hormone, showed hyperglycemia, the problems this suggested were not pursued They, however, have been seriously attacked in a telling series of experiments conducted during the past three years by

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\* In recent years it has been shown by Geiling and Eddy<sup>59</sup> that posterior lobe extract and its derived products, pitressin and pitocin, produce hyperglycemia, also by Nitzescu and Benetato<sup>91</sup> that there is a coincidental increase of inorganic phosphate in the blood

Houssay and Biasotti<sup>71</sup> who have shown that diabetes fails to develop in hypophysectomized toads on subsequent removal of the pancreas. When, however, toads in this precarious state of experimental carbohydrate balance are given subcutaneous implantations of the anterior lobe of fishes, birds or mammals, they immediately become diabetic. Though this effect is less striking in hypophysectomized dogs subsequently deprived of the pancreas, they acquire a diabetes of slow evolution with long periods of remission in which hypoglycemic crises may occur. It has also been shown by the Argentine physiologists that administration of the growth hormone to normal rats and dogs will provoke glycosuria with polyuria and hyperglycemia, and they go so far as to predict the discovery of a pituitary diabetogenic hormone which plays the predominant if not exclusive role in carbohydrate metabolism.

There is only one way of reconciling these contradictory views regarding posterior vs anterior lobe control over the utilization of sugar—and that is to accept them both as correct with another interpretation. This interpretation is that which has already been advanced as an explanation of the hypertension—namely that the pars intermedia cells pass into and activate the neurohypophysis.\*

But whatever may prove in the end to be the correct explanation, there is evidence at hand that extracts of both anterior and posterior lobe exercise an antagonistic effect on insulin. Whether this effect is produced by inhibition of the islets or by extrapancreatic neutralization of liberated insulin remains undetermined. From an histopathologic standpoint, while primary pancreatic diabetes is said to be accompanied in something over half of the cases by demonstrable lesions of the islet tissue, no corresponding changes have ever been convincingly described either in acromegaly with hyperglycemia or in the few instances of pituitary basophilism in which autopsy was performed.

All said and done, there is possibly no more reason why we should expect to find the islets appreciably atrophic in these maladies than to find them hyperplastic in the counter-states of pituitary deficiency in which the tolerance for carbohydrates is increased. Histopathology has its limitations, and the function of cells may conceivably be altered without recognizable change of form.

*The Adrenal Participation in the Syndrome*—Hypertrophy of the adrenal cortex was one of the striking features of Miss P's case as it has been of most other instances of basophilism that have had a post-mortem verification. It is chiefly shown in the zona fasciculata whose cells are distended by an increase in their lipoid content. Certain

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\* The reciprocal effects on the hypophysis of disordered function of the pancreatic islets has received scant attention from the anatomic side. Kraus<sup>75</sup> described a shrinkage of the gland particularly noticeable in the pars intermedia after pancreatectomy in the cat—an observation which others failed to substantiate. Eaves,<sup>43</sup> on the other hand, briefly reported that prolonged injection of small doses of insulin in rabbits causes enlargement of the hypophysis and changes suggesting cellular hyperplasia, both of the pars intermedia and the pars anterior.

features of the syndrome so strongly suggest a primary hyperadrenalism it is not surprising that several of the patients in the series should have been subjected to a suprarenal exploration with unilateral adrenalectomy. And the fact that a definite though small adenoma of cortical elements has been found in one or two instances has been highly misleading\*.

The basophilic elements, therefore, whatever the nature of their hormone, evidently elaborate a substance which has a highly stimulating



Fig 31—Adrenal cortex (magnification  $\times 80$ ) from *A*, the case of pituitary basophilism, *B*, an acromegalic, *C*, an adult with hypopituitarism from chromophobe adenoma, *D*, an adult pituitary dwarf, aged 27

effect on the adrenal cortex. The accompanying photograph (fig 31) indeed suggests that the degree of hyperplasia exceeds even that produced by the acidophilic elements in acromegaly. To put to a compara-

That an accessory para-ovarian nodule of adrenal tissue was found in this and another case of basophilism need cause no surprise in view of the embryogenic relation of both adrenal gland and reproductive apparatus to the wolffian body



tive test the effect on the cortex of the growth principle and of a sex-maturing principle the following study (unpublished) was made a year ago at my request by Drs Thompson and Tioppoli

For the experiment were used three groups of three immature litter-mate female rats. All nine animals were 45 days old and, with trifling variations, weighed 60 Gm apiece. Of each group of three, one member was used as a control, a second member was given twice daily a parenteral injection of 0.5 cc of a modified anterior lobe preparation, the third member was given twice daily 0.5 cc of prolactin-containing urine of pregnancy (the adeno-hypophyseal gonadotropic substance would have been preferred but none was at hand).

The intromittus of all three animals receiving prolactin opened on the fourth day, whereas this took place in the case of the three controls and of the three animals receiving growth hormone at variable times, averaging about seventeen days.

Throughout the experiment, all animals were given an ordinary diet and were killed at the expiration of seventy-two days, during which time the three control animals had gained ca. 85 Gm, those injected with growth extract ca. 120 Gm, and those injected with prolactin, an average of only 70 Gm (one of them lost weight from a slight infection).

On the fifteenth day of the experiment, the right adrenal and ovary were removed from each of the first trio, the weights of the cleanly stripped adrenals being as follows: control, 9 mg; growth hormone, 10 mg; prolactin, 112 mg.

On the forty-seventh day, the adrenals were removed from the second trio and gave the following weights: control, 16 mg; growth hormone, 22 mg; prolactin, 20.5 mg.

On the fifty-second day, the adrenals removed from the third trio gave these weights: control, 20 mg; growth hormone, 16 mg; prolactin, 27 mg.

When all nine were killed on the seventy-second day of the experiment, the animals being 117 days old, the remaining adrenal of each of the first trio weighed: control, 26 mg; growth hormone, 24 mg; prolactin, 37 mg. The adrenals of the second trio weighed: control, 36 mg; growth hormone, 45 mg; prolactin, 51 mg. The adrenals of the third trio weighed: control, 20 mg; growth hormone, 14 mg (this animal had a terminal infection); prolactin, 47 mg.

While it is known that the female rat not only has heavier pituitary glands but also heavier adrenals than the male, a disproportion which increases with age, an estimate of the weight of the normal adrenal at ca. one hundred and seventeen days is given as 20 mg (Donaldson). Needless to say, the enlargement of the organs above this weight was due solely to a cortical hyperplasia.

From this experiment, which as we shall see runs counter to the experience of others, it was deduced that among the known sex-maturing substances, prolactin at least serves as an adrenocortical stimulant.

A secondary adrenal hyperplasia was shown by Evans to be one of the striking features of experimental gigantism in the rat, while an actual cortical adenomatosis was described by Putnam and his associates<sup>99</sup> in their first example of canine acromegaly, and though we cannot be quite sure to which of the two principal hormones this change was attributable, in view of the unpurified extract that was used in these experiments, it was probably due to that of growth.

What may be the condition of the adrenals in hereditarily dwarfed mice, in which the growth factor alone is deficient, I do not know, but

when there is dual hypopituitarism (cf fig 32), whether produced by a chromophobe adenoma or by an experimental hypophysectomy affecting both elements, cortical atrophy may be extreme. It was shown by Smith<sup>115</sup> that the weights of the adrenals of hypophysectomized rats will shrink within six days to one-half the size of the controls. What is more, the atrophic glands of these animals can be promptly restored to normal or near normal by glandular implantations, which, of course, contain both growth and sex fractions.

Evans, however, finds (personal communication) that purified growth hormone by itself will restore almost to normal the atrophic adrenals of hypophysectomized rats if treatment is instituted soon after the hypophysectomy. At the same time, he is convinced that the gonadotropic substance in pregnant-mare serum and that in the urine of pregnant women have no effect whatever on the adrenal cortex (the influence of the pituitary sex principle itself was not investigated), which controverts the Thompson-Troppoli experiments just cited.

The adrenal cortex is known to be essential to life, a bilateral adrenalectomy leading to symptoms which, even to the extreme fall in

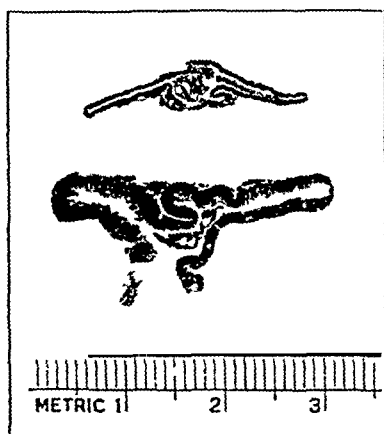


Fig 32—To compare (natural size) the atrophic adrenal cortex of adult hypopituitarism (above) produced by a chromophobe adenoma with the hyperplasia of pituitary basophilism (below) shown in this case, both persons approximately same age.

body temperature and marked loss of weight, closely resemble the acute cachexia hypophyseopriva often observed after hypophysectomy in adult dogs. Beyond this, and the fact that these symptoms may be overcome and an essentially normal condition reestablished by the injection of a cortical extract, those who have worked most extensively in the field of adrenal physiology confess<sup>122</sup> to scant knowledge of what the normal function of the cortical hormone may be.<sup>123</sup>

Of the relation of the cortex to the enclosed neuromedullary part of the gland which secretes epinephrine, we know even less than we do of the relation of the adenohypophysis to the neurohypophysis which it envelops. This admission is the more remarkable in view of the peculiar and striking syndromes which are clinically

known to accompany what presumably are primary, often malignant, adenomas of the adrenal cortex and of the chromaffin tissue of the medullary substance. Characteristic features of these syndromes are hypertension, hypertrichosis, deviations of secondary sex qualities such as the masculinization of women, and even glycosuria.

While nothing is known of the reciprocal pituitary changes accompanying these clinical states of primary hyperadrenalism, an increase of basophilic elements might be anticipated if, as stated by Kraus<sup>77</sup> and by Berblinger,<sup>21</sup> these elements are notably diminished in number in cases

of Addison's disease. However this may be, when a syndrome akin to that of hyperadrenalism occurs in association with a definite basophilic adenoma, as in the case under discussion, the hypertrophic changes in the adrenal cortex, to which the symptoms are naturally ascribed, can scarcely be interpreted as other than a secondary effect.

*Gonadal Effects*—We have seen that in this patient there was an early period of amenorrhea followed by a long interval of fairly normal menstruation, when again a two year period of menstrual cessation occurred and preceded death. The disorder therefore showed periods of symptomatic exacerbation and remission, just as hyperthyroidism or acromegaly may occur in successive waves of activity.

The ovaries, as recorded in the protocol, while essentially normal in appearance (fig 33), gave evidence of follicular stimulation in the absence of luteinization resembling in this respect the ovaries of acromegaly<sup>40</sup> and of adult rats treated with pituitary transplants.<sup>116</sup> The changes in the theca interna (fig 34), consisting of increased vascularization with an epithelioid transformation and vacuolization of the cells, are those known to occur (Corner<sup>29</sup>) during the period preceding maturation of the ovum\*. They are looked on by many as the true interstitial cells of the ovary† and while they may possibly participate in the formation of the corpus luteum, evidence seems to favor the granulosa cells as the chief source of this body. Theca cells heavily laden with lipoids appear in the corpus albicans only after granulosa cells have disappeared.

It is claimed<sup>54</sup> that the adeno-hypophysial gonad-influencing principle can be divided into two separable fractions, one having follicularizing and the other luteinizing properties. From the condition of the ovaries of this patient it would appear that the follicularizing stimulus is present but that the element to complete the ovulatory cycle with rupture and luteinization of the follicle is absent, thus accounting for

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\* Since this paragraph was written, Dr G W Corner, having kindly examined the sections, states it to be his belief that the normal processes of follicular growth have been in abeyance for some time and that the ovary resembles that of a patient in the early menopausal years. While the primordial ova are in good condition, there is a striking absence of medium-sized follicles and the granular cells of all the large follicles are in the early stage of atresia, showing breakdown of the nuclei. His assumption would be, therefore, that the ovary for some reason was not receiving its normal stimulus to cyclic growth.

† The possible relation of the interstitial cells of ovary and testis to the secondary characters of sex is a complicated and disputed subject<sup>103</sup> which cannot here be gone into, though the bearded faces of women with pituitary basophilism suggest that something in this direction is abnormal. Collip has recently shown<sup>28</sup> that when the "anterior pituitary-like hormone" of the placenta is administered to hypophysectomized male rats, the usual atrophic changes in the reproductive apparatus are limited to a degeneration of the germinal epithelium, whereas the interstitial cells are increased and the accessory sex organs fail to undergo atrophy.



Fig 33—Section of patient's ovary (magnification  $\times 5$ ) to show surface appearance, situation and number of cysts and of corpora atretica

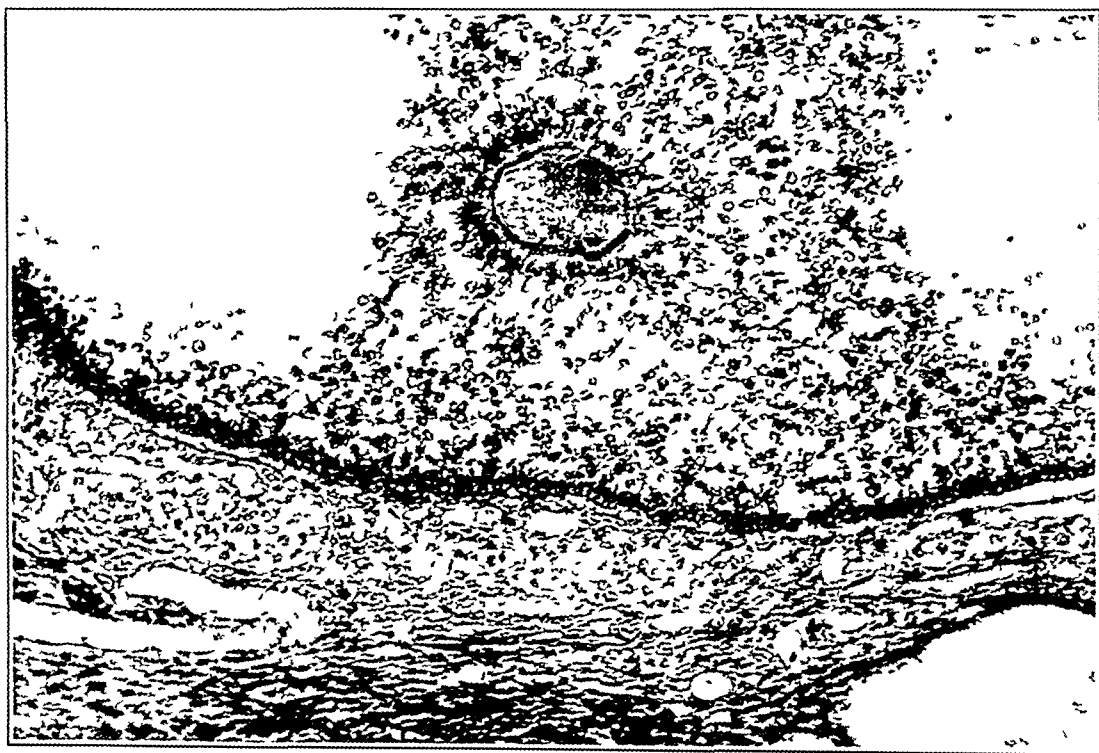


Fig 34—Degenerated oocyte in cumulus and active theca interna (magnification  $\times 150$ )

the amenorrhea. Her urine was tested on immature female rats for gonad-stimulating properties with negative effects and the same was true of another patient (case 11 of another report<sup>38</sup>) in the series. On the other hand, the urine of the young girl whose photographs have been shown (cf fig 14) proves to have a follicularizing effect on young rabbits, so that some more sensitive recipient than the rat—the ring dove, for example<sup>108</sup>—may be necessary for the detection of these substances.\*

The patient's small uterus with its thin atrophic endometrium was the opposite of that seen in acromegaly, both clinical<sup>125</sup> and experimental,<sup>99</sup> an enormous hyperplasia of vagina, uterus, tubes and endometrium being characteristic of these states.

As already pointed out, the evidence to show that the basophilic cells are concerned with the gonadotropic hormone is contradictory and inconclusive. Just what would be the somatic effect of prolonged administration of the adeno-hypophyseal sex principle by itself is unknown and for the same reason it is unknown what changes would be produced in the ovary and reproductive tract by such long continued stimulus. Excessive luteinization of the ovary was shown by Evans and Long<sup>50</sup> (1921) to follow the prolonged administration of their original growth extract. But since the preparation then employed was not free of the gonadotropic principle, this was a complicating factor in the early experimentally produced states of gigantism both in rats and dogs and largely explains the associated gonadal effects that were observed.

Even though from the adeno-hypophysis of the sheep an active sex hormone may be prepared, it proves not to stimulate the ovulatory mechanism in the same way in all species, so that experimental data will scarcely be transferable to man until animals higher in the series<sup>64</sup> (possibly in the end, anthropoids) are employed. The whole subject has become further complicated and attention has been distracted from the pituitary hormone to the study of similar substances more easily obtained. This was brought about by Aschheim and Zondek's discovery<sup>6</sup> of a sex-maturing product (prolan) in the urine of pregnant women, numerous substances with similar properties having since been found in other body fluids or tissues in varying concentrations in different animals. Whether these several substances are the same as the pituitary hormone, as some take for granted, or merely serve as activators of it,<sup>51</sup> or represent products derived from it, or have nothing to do with it other than that their biologic effect on maturation is similar will not be known until the precise chemical formula of each comes to be worked out.

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\* In appraising these reactions, it should not be overlooked that those competent to pass on the question of separate follicle-stimulating and luteinizing hormones do not feel that there is adequate evidence of their separate existence.

Meanwhile, in view of their variable source of origin and variable action on different species, they have, if anything, served temporarily to confuse rather than to simplify our understanding of the direct pituitary influence on the peculiar chain of events concerned with the ripening, discharge, insemination and implantation of the ovum. It is a delicate mechanism easily disturbed. And while the condition of the ovary might be expected to give evidence of the nature of the product elaborated by a basophilic adenoma, in the present state of our knowledge its pathologic and symptomatic effects are difficult to appraise.

While fully believing that the adenohypophysis is the root of all this evil relating to disturbances of growth and sexual activity, it seems almost too much specifically to charge it with thyroid-activating, glyco-genic, lactogenic, metabolizing, follicle-stimulatory, pigment-affecting, luteinizing and menstrual-initiating properties and other petty crimes of like sort for which its subordinate accomplices may well enough be responsible.

### CONCLUSIONS

During the past two decades, much has been learned about pituitary dysfunction from many angles—from comparative and experimental zoology most of all, from clinical pathology a great deal, something from histologic cytology, and as yet, all too little from biochemistry to which we pin our chief hope.

Whereas the pituitary body was once looked on as a functioning whole, this idea was disrupted when Howell showed in 1898 that its blood pressure-raising effect was confined to extracts of the posterior lobe. Since then, an ever mounting number of properties suggesting separate chemical messengers have come to be ascribed to one or another subdivision of the gland—those of the posterior lobe giving acute pharmacodynamic responses, those of the anterior lobe producing their effects more slowly.

After Howell's discovery, fifteen years passed before it was found that posterior lobe extracts could control diabetes insipidus, and ten years more before the relation of this disorder to certain clusters of nerve cells in the hypothalamus was appreciated. And now after a lapse of thirty-five years, the fact that posterior lobe overactivity may be responsible for a number of hitherto obscure clinical disorders has only begun to be realized.

Attention meanwhile has been chiefly focused on the properties of anterior lobe extracts whose remarkable effects have served further to emphasize the dominance of the gland over other members of the endocrine series. Much, indeed, that has already been done in studying these subsidiary glands as isolated and independent structures needs redoing and reinterpreting. And at the same time the conception that anterior lobe, posterior lobe and interbrain work in harmony and cannot well be studied separately has been clearly demonstrated.

The pituitary adenomas have been made the subject of this lecture with the intent of drawing renewed attention to these processes as secretory "stills" which, in spite of their pathologic structure, nevertheless in all probability are elaborating an excess of the normal hormones. Not until we have learned how to incite in experimental animals an actively and continuously secreting lesion of this sort can we expect precisely to reproduce, and thereby fully to interpret the effects of Nature's prolonged experiment on man.

In order to gauge what substance if any is secreted by the different adenomas, the patient's blood and urine as well as tissue from the tumor itself when available will some day have to be tested for the presence of each of the accepted as well as of the several predicated hormones of the normal gland. But only when these tests come to be more simplified than they now are will it be possible definitely to say whether a chromophobe adenoma, like that of the dwarfed child, actually has any secretory product, whether the overgrowth in lads like those described is due to an excess of the growth principle, whether or not the blood of the acromegalic woman was flooded with a separable lactogenic hormone, and what may have been the nature of the substance elaborated by the tumor in the case of the unfortunate young woman so long victimized by pituitary basophilism.

But however much of all that I have said regarding these adenomas and their secretory effects may be fact and how much fancy, we may be sure that in the course of time the greater part of it will be modified out of all recognition. Consequently, should this second lecture on dyspituitarism prove twenty years hence to have contained a modicum of truth, so helpful to our further understanding of pituitary function in disease as was the attribution of adiposogenital dystrophy and retardation of growth to pituitary insufficiency, that would be recompense enough for me and sufficient justification, I hope, for the act of the Harvey Society.

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# PERIDUODENITIS AND PERICHOLECYSTITIS

AN ANATOMIC, CLINICAL AND ROENTGEN STUDY OF ADHESIONS  
IN THE UPPER RIGHT QUADRANT

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AND

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DETROIT

A number of articles have appeared in recent years emphasizing the clinical significance of adhesions in the upper right quadrant. Recently the French authors, Duval, Roux and Beclère, exhaustively treated the subject of adhesions in this area in a book, "The Duodenum," in which they described anatomic, clinical and roentgen findings. They suggested operations for severance of adhesions and short-circuiting of obstructed points.

Our study arose from an attempt to apply clinically the recorded data on this subject. If the clinical and anatomic entity is as definite as has been described, it was felt that careful study of a rather large gastro-intestinal material should reveal a number of such cases.

We are concerned here with adhesions about the first and second portions of the duodenum and about the gallbladder, and their clinical significance. Lesions of the third and fourth portions of the duodenum and duodenal stasis in these portions are not dealt with.

## RESUME OF LITERATURE

Attention was first called to this subject from a clinical point of view by Dr Robert T Morris<sup>1</sup> in an address given before the Wayne County Medical Society (Detroit area) in May, 1905. He advanced the theory that these adhesions were inflammatory and of probable biliary origin. The symptoms were those of upper abdominal dyspepsia with some resemblance to those of peptic ulcer. The treatment that he advocated was separation of the adhesions and removal of the gallbladder.

Konjetzny<sup>2</sup> in 1913 first doubted the inflammatory origin of these adhesions, as he demonstrated them in the new-born and in infants in from 15 to 20 per cent of autopsy specimens. He stated that traction

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From the Detroit College of Medicine and Surgery and the North End Clinic.

The work on simultaneous cholecystography and gastro-intestinal roentgenography was aided by the North End Clinic Research Fund.

1 Morris, R T. Gall Spider Cases, *Am Med* **10** 95, 1905.

2 Konjetzny, G E. Ueber anomale ligamentaere Verbindungen der Gallenblase und ihre klinische und pathologische Bedeutung, *Med Klin* **9** 1586, 1913.

of the colon on the gallbladder by means of the hepatocolic band would, by mechanically angulating the gallbladder neck, produce obstruction of the outflow of bile and hence colic. He also mentioned duodenopyloric stenosis due to the hepatocolic band crossing the duodenum.

Harris<sup>3</sup> in 1914 reported 6 cases of periduodenal bands. The symptoms in these cases resembled those of ulcer. There were also sharp attacks of pain in the upper right quadrant suggesting gallstones. He independently ascribed a congenital origin to these bands rather than the inflammatory origin proposed by Morris.

Cole<sup>4</sup> called attention to duodenal deformity caused by veils, and advised that in deformed cap not due to spasm, one is justified in making a diagnosis of an organic lesion which "may be due to ulcer, gall bladder adhesions or a veil, the weight of evidence being in favor of the one it most closely resembles."

Taylor<sup>5</sup> reported a large series of cases in which he concluded that membranes about the duodenum frequently cause partial obstruction by angulation and constriction. He stated that the best study of this region is by roentgenography, which indicates function rather than the anatomic distribution of the adhesions.

Cromarty<sup>6</sup> ascribed to these cases an ulcer-like picture but differing in that the pain tends to be persistent and is unrelieved by the ingestion of food. The diagnosis is made by irregular filling of the cap.

George and Leonard<sup>7</sup> in 1922, in a monumental work, demonstrated the relation of the diseased gallbladder as outlined by stones to the duodenum and pylorus. They emphasized the importance of the indirect signs, which up to this time were the only practical means of diagnosing cholecystitis by roentgenographic methods.

Duval, Roux and Béchère<sup>8</sup> in 1928 reported an exhaustive study of adhesions about the duodenum. They divide them into (1) periduodenitis of biliary origin, demonstrated by deformity of the bulb region due to cholelithiasis and cholecystitis, which may even persist after cholecystectomy, and (2) essential periduodenitis, in which no cause for the production of adhesions is found, the gallbladder, duodenum, appendix and greater omentum all being normal. In the latter group

3 Harris, M. L. Constrictions of the Duodenum Due to Abnormal Folds of the Anterior Mesogastrium, *J. A. M. A.* **62** 1211 (April 18) 1914.

4 Cole, L. G. Veils in the Right Hypochondrium and Their Differentiation from Other Organic Lesions and Spasms, *Am. J. Roentgenol.* **9** 137 (March) 1922.

5 Taylor, A. S. Anomalous Abdominal Membranes. Their Influence upon the Digestive Tract, *Ann. Surg.* **75** 513 (May) 1922.

6 Cromarty, R. P. Surgery of Duodenal Membranes, *Canad. M. A. J.* **12** 876 (Dec.) 1922.

7 George, A. W. and Leonard, R. D. The Pathological Gall Bladder, Roentgenologically Considered, New York, Paul B. Hoeber, Inc., 1922.

8 Duval, P., Roux, J.-C., and Béchère, H. The Duodenum, Medical Radiologic and Surgical Studies, St. Louis, C. V. Mosby Company, 1928.



they placed the cases described by Morris, Harris, Cole, Cromarty, Taylor and others. Essential periduodenitis reveals itself by an aggregation of many symptoms which individually show nothing characteristic of the lesion. There are three types of symptoms: (1) those resembling the symptoms of duodenal ulcer, with pain immediately or from four to five hours after eating but unrelieved by food or alkali and associated with nausea, (2) those resembling the symptoms of biliary colic and accompanied by vomiting and perhaps even diarrhea and jaundice, and (3) nonlocalizing symptoms suggesting neurasthenia aggravated by malnutrition and progressive emaciation.

These authors have little confidence in the medical treatment of these membranes, but they stated that the mere presence of membranes about the duodenum does not warrant surgical intervention. The clinical and roentgenologic syndrome of duodenal stenosis must be present. They advise against simple section of the membranes because of their tendency to reform, and prefer instead short-circuiting operations when definite stasis is present.

Harvey<sup>9</sup> in 1918 made an intensive study of peritoneal folds and reviewed the literature. He gave a table showing that a cystocolic ligament was found by nine different authors in from 15 to 30 per cent of routine autopsies. He himself found the ligament in 18 per cent of cases, including only those cases in which the ligament extended up the gallbladder more than one-third its length. Ancel and Lencert<sup>10</sup> found the ligament well developed in 48 per cent of routine autopsies, and in some instances it completely closed the foramen of Winslow. In 1923, Nagel,<sup>11</sup> of the Mayo Clinic, found ligaments extending from the gallbladder to the duodenum and colon in 25.3 per cent of 150 consecutive necropsies.

Clairmont and Meyer,<sup>12</sup> of Zurich, divided abdominal adhesions, excluding those of fluid peritonitis, into: 1. Adhesions secondary to a primary inflammation of an organ, such as ulcer of the stomach or duodenum, inflammation or stones of the gallbladder, etc. 2. Adhesions with no disease of neighboring organs, which they termed "perivisceritis." This leaves the origin of the adhesion open and avoids the impression of a spontaneous adhesion. Examples of perivisceritis are periduodenitis, pericholecystitis and perigastritis. 3. Postoperative adhesions. Congenital bands would be classified under perivisceritis.

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<sup>9</sup> Harvey, S. C. Congenital Variations in the Peritoneal Relations of the Ascending Colon, Cecum, Appendix and Terminal Ileum, *Ann Surg* **67** 641 (June) 1918.

<sup>10</sup> Ancel and Lencert, quoted by Nagel.<sup>11</sup>

<sup>11</sup> Nagel, G. W. The Etiology and Importance of the Cystico-Duodeno-Colic Fold, *Surg, Gynec & Obst* **37** 363 (Sept.) 1923.

<sup>12</sup> Clairmont, P., and Meyer, M. Bauchfellverwachsungen, *Arch f klin Chir* **157** 474 (April) 1929.

or would need a fourth classification. These authors reported 20 personal cases of periduodenitis, in 17 of which the patients were operated on with good results and in 3 of which there was no change after the operation.

After a recital of the manifestations of abdominal adhesions by all data, Clairmont and Meyer added that a necessary part of the examination is the exploration of the psyche, 62 per cent of their patients having had a psychic defect. They concluded that even extensive adhesions after cholecystectomy do not lead to adhesion pains. Roentgenograms that indicate periduodenitis, traction, adhesions and constriction are seldom free from objections. The authors advised prudence in attaching clinical significance to the deviations found roentgenologically.

Payr, in a discussion following the presentation of Clairmont and Meyer's paper before the German Surgical Society, summarized the problem of adhesions in the following question: Are the patient's complaints caused by adhesions, are other hitherto unknown diseases present or is there perhaps a psychic condition that causes the complaints?

Renzi agreed with Clairmont that adhesions follow operations on the upper part of the abdomen most frequently, whereas cases of ileus most frequently follow operations on the lower part of the abdomen, particularly in the pelvis.

In summary, then, there is no disagreement with the fact that these adhesions occur frequently. Whether they are of congenital or of inflammatory origin has involved dispute. There is also considerable disagreement as to whether they cause symptoms. Most of the articles record cases in which symptoms have been produced and operations resorted to, but the follow-up observations in some of the cases recorded leave doubt as to the permanence of the improvement and the psychic balance of the patient.

Our plan of study included (1) anatomic data derived from autopsy, (2) roentgen study of the right upper quadrant by simultaneously filling the gallbladder and duodenum and (3) clinical investigation.

#### ANATOMIC DATA

It was considered essential from the very first to distinguish between congenital membranes in the upper right quadrant, the presence of which is mentioned in a somewhat "step-motherly" fashion by the anatomists, and true inflammatory adhesions. With this in mind a series of 54 adult specimens were dissected. Eleven of these were examined at autopsy.<sup>13</sup> The remaining 43 were cadaver specimens,

<sup>13</sup> Through the courtesy of Dr. Osborne A. Brines, pathologist to the Receiving Hospital.

in which the condition of the abdominal cavity was examined previous to dissection<sup>14</sup> Table 1 summarizes the results of these examinations

From these dissections we can describe the normal anatomic relation of organs and membranes in the upper right quadrant as follows (fig 1 *A*)

The lesser or gastrohepatic omentum attaches the lesser curvature of the stomach to the liver. Its right lateral margin generally reaches to only the first or second centimeter of the duodenum, i. e., as far as the portal vessels. It then winds around the vessels and is reflected backward and to the left to form the anterior layer of the lesser

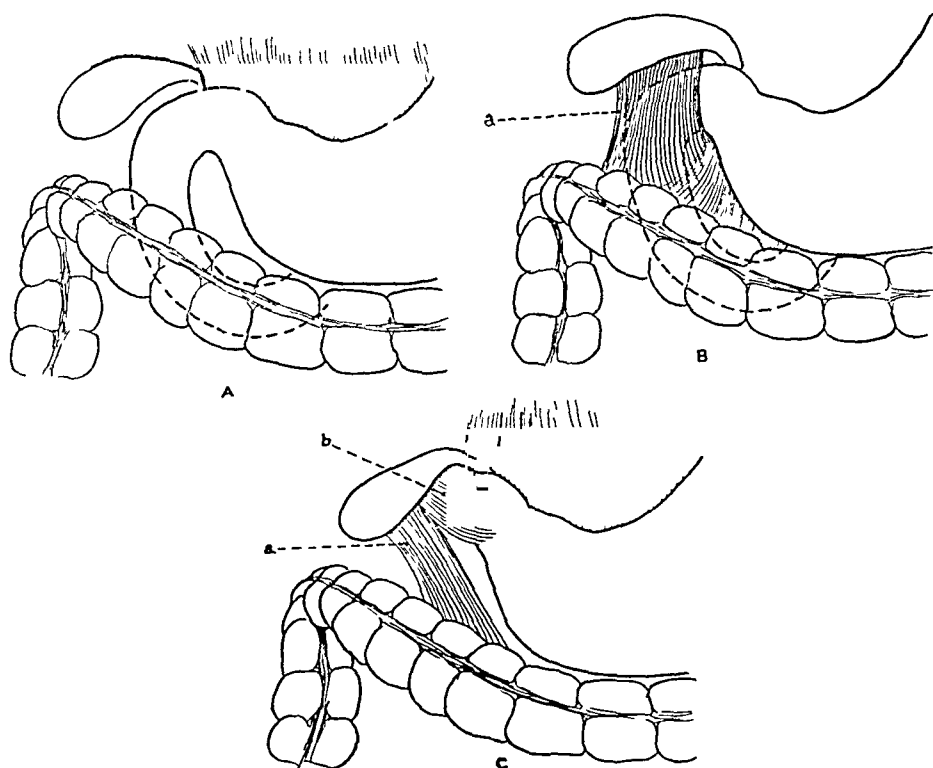


Fig 1—*A*, normal relations in the upper right quadrant, *B*, drawing showing (*a*) cholecystocolic fold, *C*, drawing showing (*a*) cholecystocolic fold and (*b*) cholecystoduodenal fold

peritoneal sac. As it winds about the portal vessels it becomes the anterior boundary of the foramen of Winslow.

If the lateral margin extends further to the right it invests the gallbladder neck above and the first and second portions of the duodenum below, forming the cholecystoduodenal fold (9 cases). If it is continued still further to the right it invests the gallbladder fundus above and the transverse colon below, forming the cholecystocolic fold.

14 Through the courtesy of Drs. C. F. McClintic and Watson Beach of the anatomic department of the Detroit College of Medicine and Surgery.

(14 cases) The cholecystocolic fold is a definite thin flat membrane which lies in the plane of the gallbladder, most frequently almost in a sagittal plane. Below it inserts and fuses with the anterior layer of the greater (gastrocolic) omentum, above its extension attaches the gallbladder fundus to the liver, and a further prolongation to the right is attached to the liver itself (fig 1 *B*). In 5 cases a band was found running from the colon below, attaching above to that portion of the liver behind the gallbladder and not investing the gallbladder, a hepatocolic fold. All possible variations of these folds were seen, as will be noted from the table.

It will be noted from figure 1 *A* that the transverse colon normally crosses the descending duodenum at its midportion. The duodenum in this situation is very thin-walled and collapsible. In autopsy specimens it is usually impossible to distinguish it from the retroperitoneal tissue by rolling under one's finger or by simple inspection. If, however, one forces some air into it from the stomach, its outline will be visible.

TABLE 1—*Membranes in the Right Upper Quadrant in Fifty-Four Cadaver and Autopsy Specimens*

	Number of Cases	Per Cent
Cholecystocolic	22	41
Hepatocolic	29	54
Hepatocolic plus cholecystocolic	8	
Inflammatory adhesions	1	
Of biliary tract origin	14	
Of pelvic inflammatory origin	5	
	1	
	3	5

In this situation, therefore, it is easy for pressure of the transverse colon, especially if distended, to occlude the duodenum. Duval, Roux and B  cl  re laid great stress on this anatomic arrangement, stating that this is a frequent cause of duodenal stasis.

In view of the frequency with which the cobwebs were found unrelated to other pathologic changes in the upper right quadrant, their presence in the new-born and in infants and their almost constant anatomic arrangement, it is difficult for us to ascribe clinical significance to them. The anatomic relation of the colon to the gallbladder by traction of adhesions and to the duodenum by pressure on its second portion may explain why patients with malfunction of the gallbladder and duodenal disease obtain relief from emptying of the colon by cathartics, enemas and the horizontal position.

It is important, however, that these cobwebs be borne in mind and recognized (1) to realize their frequency and therefore, in an exploration of this region, not to be misled into believing that they are inflammatory, a cause of symptoms and an indication for removal of the gallbladder, (2) to distinguish them from the inflammatory adhesions

There were 3 such cases in this series, 2 of cholecystic origin and 1 of pelvic inflammatory origin. This last case, in a colored woman, was interesting. The entire pelvis was frozen into a mass of adhesions, the uterus being retroverted and fixed. There were numerous filmy adhesions, not in definite bands, uniting the colon to the under surface of the liver and the anterior wall of the abdomen, the colon to the gallbladder, the gallbladder to the duodenum and the stomach to the under surface of the liver. After separating these adhesions a normal anatomic relation of the lesser omentum was found, with a well marked foramen of Winslow and a normal gallbladder, indicating the absence of congenital membranes.

#### ROENTGEN STUDY

In an attempt to demonstrate the changes in the contour of the cap and other viscera as a result of pericholecystic and cholecystic diseases, we examined roentgenologically a number of patients by simultaneously filling the gastro-intestinal tract with barium while the gallbladder was

TABLE 2—*Data on Simultaneous Visualization of the Gallbladder and Gastro-Intestinal Tract*

	Number of Cases
Gallbladder seen with stomach and duodenum	38
Gallbladder seen with colon	31
Gallbladder seen with stomach or colon	55
Stone shadows seen with stomach and duodenum	6
Deformed gallbladder seen with stomach and duodenum	2

filled with opaque dye. The anatomic relationship between the stomach, duodenum, bowel and gallbladder was made out satisfactorily in 55 cases (table 2).

Of these there were 6 cases in which positive or negative gallstone shadows were seen and 2 in which the gallbladder was deformed. The remaining 47 were normal.

It is obvious that adhesions cannot be studied in the majority of cases of cholecystitis by this technic, as the gallbladder cannot be visualized. The exceptions to this are the cases in which positive or negative stone shadows are found.

In the first group of cases the position of the stomach and duodenum as related to the gallbladder was studied. The gallbladder was usually found lying to the right and close to the duodenal cap and pylorus. In a very small percentage of cases the gallbladder was distant from the cap. In one instance this separation was 5 cm. On the whole, the relationship was quite constant, more so than the relationship to the vertebrae given in anatomic textbooks.

An attempt was made to apply Whittaker's technic of fluoroscopic examination of the stomach, duodenum and filled gallbladder. The

latter could not be visualized by fluoroscopy in enough cases to make this a practical procedure. However, it was possible to make use of one sign, namely, localized tenderness over the gallbladder, when the latter could be seen.

In a few cases a normal gallbladder, as demonstrated by a normal cholecystogram, produced a "seat" or impression on the duodenum. Conversely, the diseased gallbladder often failed to produce a seat. However, a seat was seen in many cases of cholecystitis, so that the presence of a seat, although not pathognomonic of cholecystitis, still may be suggestive of disease of the gallbladder.

We then studied the relationship of the gallbladder to the colon and intestines. This was done by examining the patient five hours after the barium meal, twenty-four hours afterward and after the opaque enema. The gallbladder dye was usually given at night before the patient appeared for this test. Examinations were made in the prone and upright position. The relationship of the gallbladder to the colon was fairly constant. It rested on the transverse colon about 2 or 3 cm. to the left of the hepatic flexure. It usually accompanied the colon upward in the prone position and downward in the upright position, although in 1 case the gallbladder extended below, and in another it was 3 cm. above, the colon. In some cases the gallbladder as well as the colon was found in the pelvis when the patient was upright. In most instances there was an excursion of 4 or 5 cm. between the upright and prone position.

Formerly a high hepatic flexure was considered to be one of the indirect signs of disease of the gallbladder. This study clearly demonstrated that there is no basis for such a belief, for the liver, gallbladder and colon are closely related and our anatomic study shows that normally some adhesions may be present. Also there frequently exist cholecystocolic and hepatocolic bands. A high hepatic flexure may indicate that the liver does not drop freely when the patient is in the upright position, but this has no bearing on cholecyctic disease.

Some data were accumulated to see if, by making the Graham-Cole test on the day the colon or stomach was studied, a day could be saved in the duration of the examination. It was found that this was impractical, as the gallbladder was partially covered by the colon, stomach or duodenum. However some interesting roentgenograms were obtained which showed the entire "*Wetterwinkel*" (weather-corner of the abdomen or upper right quadrant), including the stomach, duodenal bulb, hepatic flexure of the colon and gallbladder.

In the 2 cases showing a deformed gallbladder no abnormal adhesions to the surrounding viscera could be made out.

Briefly, then, the simultaneous method is valuable in demonstrating the anatomy of the upper right quadrant. Theoretically it should be

ideally suited to showing adhesions in this region. Practically, however, the latter use can be made only in the relatively few cases in which the diseased gallbladder can be visualized (by the presence of positive or negative shadows)

#### CLINICAL INVESTIGATION

All gastro-intestinal cases in which a roentgenologic study was made at the North End Clinic in 1930 and 1931 were observed carefully for

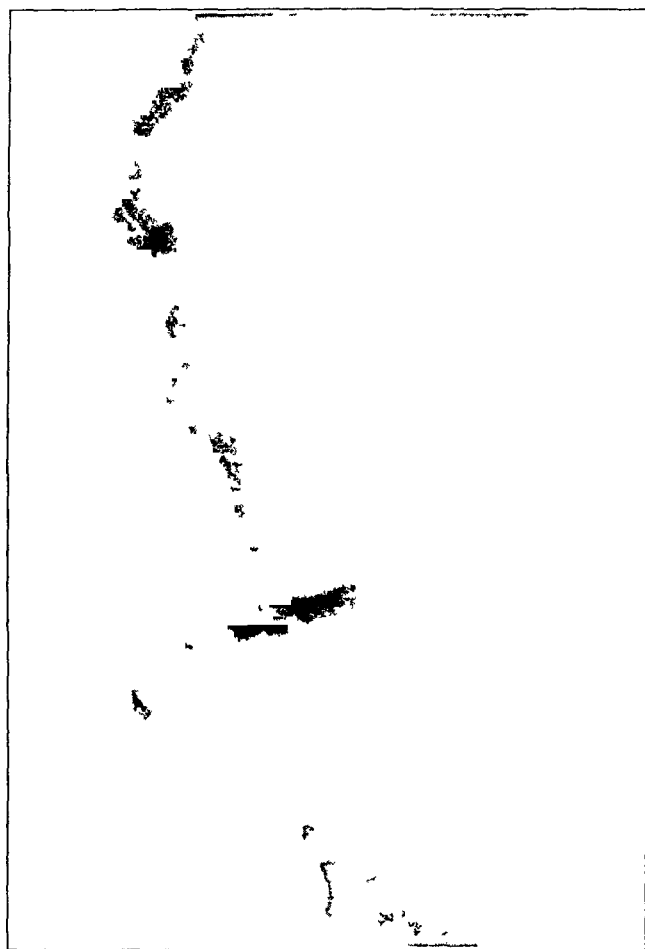


Fig. 2—Roentgenogram showing “Wetterwinkel” (weather corner) with stomach, duodenum, gallbladder and colon

evidence of adhesions in the upper right quadrant in the routine examination. In this period a gastro-intestinal study and a Graham-Cole test were made in 323 cases, a gastro-intestinal study but no Graham-Cole test in 21 and a Graham-Cole test but no gastro-intestinal study in 68.

It was thought that with adequate clinical data, combined with the roentgenologic observations, a study of this material should reveal a number of cases of pericholecystitis and periduodenitis. These cases

were carefully reviewed, with the following points in mind (a) to determine whether a deformed gallbladder indicates adhesions in the upper right quadrant, (b) to study duodenal deformity with special attention to the causes, and (c) to determine the frequency and type of duodenal deformity in all cases of disease of the gallbladder seen in the last four years at our clinic

(a) *Deformed Gallbladder*—Of the 391 gallbladders studied roentgenologically, 15 were deformed, an incidence of 4 per cent. A review of these cases showed that they were associated with the following clinical conditions: chronic cholecystitis, 4 cases, postoperative adhesions after cholecystostomy, 1 case, duodenal ulcer, 2 cases, colonic or appendical disease, 7 cases, and psychoneurosis (normal gastrointestinal tract), 1 case. A kinking deformity of the gallbladder seen in one roentgenogram may be found to have disappeared in a subsequent roentgenogram.

TABLE 3—*Causes of Duodenal Deformity*

	Number of Cases	Per Cent
Duodenal ulcer	22	42
Duval type of deformity with cholecystitis	9	17
Duval type of deformity with syphilis (syphilis of the liver?)	2	4
Duval type of deformity with nondescript symptoms	10	19
Irritable cap with cholecystitis	3	6
Irritable cap with nondescript symptoms	6	12
Total	52	100

From these figures it will be seen that in only one third of the cases of deformed gallbladder was cholecystitis of clinical degree present, in approximately one half of the cases no pathologic changes were present in the upper right quadrant.

The diagnosis of pericholecystic adhesions derived from a deformed gallbladder should arouse the thought not only of inflammatory adhesions due to cholecystitis, but also of congenital membranes, artefacts and adhesions due primarily to duodenal disease. Deformity of the gallbladder per se is not of diagnostic but only of suggestive importance, and in the absence of confirmatory data should have little significance.

(b) *Deformed Duodenum*—Table 3 shows an analysis of all cases of deformed duodenum found in the two year period. There were 52 cases shown in the 344 gastro-intestinal roentgenograms, an incidence of 15 per cent.

There are four types of duodenal deformity: (1) niche, pathognomonic of ulcer (Haudek-Akerlund), (2) constant deformity—the filling defect of L. G. Cole, probable ulcer, (3) shifting deformity of Duval—periduodenal adhesions, (4) irritable cap—spasm of local or distant origin.



Duval's deformity is differentiated from ulcer deformity in that the latter is constant in any one segment of the cap, whereas the former is shifting. Duval's deformity is differentiated from irritable cap in that in the former the cap is filled, but the deformity occupies a varying segment of the cap and is still irregular after atropine. Irritable cap, on the other hand, may fill poorly at times and be well filled at others, when filled, the contour is normal. Atropine will help to complete filling.

There were many more cases of irritable cap than are listed here, the ones included were thought at one time to be due to organic disease in the region of the cap, but further clinical and roentgen observation enables us to place them definitely in the functional group.

Of the 52 duodenal deformities, ulcer accounts for about 40 per cent, cholecystic disease, for about 25 per cent. This group represents periduodenal bands or irritable caps. The primary pathologic change here is in the gallbladder, and the periduodenal lesion is incidental.

The remainder, approximately 30 per cent, represents a group in which no ulcer or pathologic change in the gallbladder could be demonstrated. The duodenal deformity is shifting and inconstant. There is no duodenal stenosis or retention. The symptoms do not fit the roentgen observations, the final diagnosis in these cases being constipation, psychoneurosis, etc. No clinical entity could be built up from the symptoms in these cases. Our impression is that the periduodenal lesion is not significant clinically.

In general, the periduodenal adhesions have the same relation to duodenal disease as have pericholecystic adhesions to disease of the gallbladder; in the presence of normal duodenal function we can disregard the periduodenal deformity. It is necessary to bear in mind, when discussing periduodenal adhesions, that they may have their genesis in other organs than the duodenum, i. e., the gallbladder, the colon, congenital bands, abdominal lymph glands, inflammations, etc.

(c) *Disease of the Gallbladder*.—A study was made of all the cases of definite biliary disease seen in the clinic during the four year period from 1928 to 1931 inclusive. Some of the cases of cholelithiasis had to be omitted from this study because there were no accompanying gastro-intestinal roentgenograms. The high ratio of cholelithiasis to cholecystitis (24/42) is accounted for because only cholecystitis with definite clinical and roentgen findings was included. The cases of cholecystitis were diagnosed at operation or showed a definite clinical history, two oral Graham-Cole tests with a nonfilling gallbladder and a negative gastro-intestinal roentgenogram.

Table 4 represents a summary of the duodenal findings in disease of the gallbladder.

It will be seen from table 4 that in 13 cases, or approximately 20 per cent, there was definite duodenal deformity, presumptively from periduodenal adhesions of biliary origin. In 7 of these cases (4 of the cases of cholecystitis and 3 of those of cholelithiasis) the duodenal deformity was of such an extent that from the roentgen indications in the duodenum alone a diagnosis of duodenal ulcer would surely have been made and in several cases this diagnosis was made until the biliary lesion was uncovered. One patient had a 20 per cent gastric residue at five hours, another showed a widened pyloric ring. It is difficult to distinguish these cases from those of ulcer by gastro-intestinal roentgenograms, but if we know that biliary disease is present (demonstrated by positive or negative shadows or a nonfilling Graham-Cole test) we can discount the duodenal findings. The possibility of a multiple lesion is present but the condition warrants removal of the gallbladder in any event.

TABLE 4—*Summary of Duodenal Findings in Disease of the Gallbladder*

	Cases of Chole- lithiasis	Cases of Chole- cystitis	Total	Percentage
Normal duodenum	18	28	46	69.7
Irritable cap	0	4	4	6
Gallbladder sent	1	1	2	3
Filled ampulla of Vater	0	1	1	1.5
Deformed duodenum (periduodenitis)	7	8	15	19.8
Total	24	42	66	100

## CONCLUSIONS

An attempt was made to apply clinically information on adhesions in the upper right quadrant in cases observed in the last two years.

The upper right quadrant abounds in membranes, as demonstrated in routine examination of cadavers. A knowledge of the presence and frequency of these adhesions is necessary to prevent too much importance being ascribed to them.

Simultaneous visualization of the gallbladder, stomach and duodenum is a method that adds little to the study of these adhesions. Where the adhesions are of biliary origin the lack of filling of the gallbladder makes simultaneous visualization infrequent.

Pericholecystic adhesions, as revealed by a deformed gallbladder, seem to be of little pathologic significance unless there is accompanying definite evidence of biliary disease.

About 20 per cent of the cases of definite cholecystitis and cholelithiasis show a shifting or definite deformity of the cap. In these cases the study of roentgenograms of the gallbladder is much more illuminating than study of the cap deformity.

The three common causes of cap deformity were found to be ulcer, cholecystitis and "essential periduodenitis." The last-mentioned diagnosis is made after excluding the two others.

Minor cases of periduodenitis occur frequently. In our experience they give rise to no tell-tale clinical syndrome. They can be recognized by means of roentgenograms, which show a duodenal deformity, usually of the shifting type, and are unassociated with stenosis or stasis. The condition does not call for surgical intervention. An acquaintance with the condition is desirable, however, to prevent its being mistaken for more serious disease in the upper part of the abdomen.

Major cases of essential stenosing periduodenitis (excluding those of biliary origin) occur rarely and are of clinical significance. We were unable to find any proved cases in our material in the past two years.

# ACROPACHY

## SECONDARY SUBPERIOSTEAL NEW BONE FORMATION

HENRY M THOMAS, JR., M.D.

BALTIMORE

Hypertrophic pulmonary osteo-arthropathy, as the syndrome is commonly designated in this country, has recently been observed under circumstances different from any heretofore described. A patient whose history I shall give in some detail returned to the clinic following an operation of subtotal thyroidectomy presenting most exaggerated clubbed fingers and swelling of the lower part of the legs. Roentgenographic studies of the bones revealed a remarkable picture of subperiosteal new bone formation, involving most of the long bones of the skeleton but showing a change in the bones of the hands which had not been seen by the clinicians or the roentgenologists at the Johns Hopkins Hospital. Since finding in an article by Holthusen<sup>1</sup> the print of an x-ray picture of a hand showing similar changes, I have come across quite a number of articles, particularly in the German literature which discuss this condition at great length. The cause of the change in the bones remains obscure, but the case to be reported throws new light on the etiology and for that reason seems to me to be of unusual interest.

### REPORT OF A CASE

*History*—W. C., a colored man, aged 22, was admitted to the Johns Hopkins Hospital on Nov. 30, 1926. For two years previous to his entrance to the hospital the patient had suffered from increasing nervousness. This was associated with a tremor which, after about nine months, caused him to abandon his work as a painter. At this time palpitation of the heart was annoying and often kept him awake at night. He was restless. Although he was becoming noticeably thinner, his neck increased in size, and he changed to a larger collar on three separate occasions. His eyes bulged. In September, 1926, he had an attack of tonsillitis which kept him in bed for three weeks and left him with marked shortness of breath on exertion, swelling of the ankles in the evening (although they were quite normal by morning) and a cough with yellow sputum. The cough, combined with a ringing in the ears, prevented sleep for about three weeks before admission. He thought that in the past two years he had lost alto-

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Read before the American Climatological and Clinical Association, May 7, 1932.

From the Medical Department and the Thyroid Clinic of the Johns Hopkins Hospital.

1 Holthusen, H. Ueber einige Besonderheiten der Osteoarthropathie (Periostitis hyperplastica) bei Heranwachsenden, Beitr. z. path. Anat. u. z. allg. Path. 77: 318, 1927.

gether 65 pounds (29.5 Kg), although his appetite had been good. He had had a moderate diarrhea for the last two months. During the month of August he took 1 drop of iodine a day without apparent effect on his condition.

The past history was uninteresting, except for frequent attacks of colds and a case of gonorrhea five years previously (1921). There was no history of primary or secondary syphilis.

*Examination*—Physical examination, made by medical intern J. H. H., showed that the temperature was 99.8 F, the pulse rate was 124, the respiratory rate was 28, the blood pressure was 156 systolic and 78 diastolic, the height was 5 feet and 8 inches (172.7 cm), the weight was 110 pounds (49.9 Kg).

The patient was more than 40 pounds (18.1 Kg) underweight, he appeared emaciated. He was restless and had a staring expression.

The skin was hot and moist, the nail beds were pale.

There was a fine tremor of the fingers. There was no clubbing of the fingers, evidence of weakness or tenderness over any bone or joint.

There was a deviation of the third thoracic vertebra to the right. The ankles were moderately swollen, with pitting edema which extended over the tibiae. The edema of the ankles was rather firm and pitted with difficulty in spite of marked swelling.

No lymph glands were palpable, except one in the right groin, which was 1.5 by 1 cm.

The patient had marked exophthalmos, there were jerky movements and a marked lid-lag. Convergence was normal. There was tremor of the closed eyelids, with widening of the palpebral fissure on focusing vision. The pupils reacted normally. The eyegrounds were normal.

The nasal septum was intact.

The teeth were in good condition.

The tonsils were large, there was a mucopurulent discharge on the postpharyngeal wall.

The thyroid gland was markedly enlarged, more so on the right than on the left. There was a palpable thrill over the right upper pole, and a to-and-fro murmur was heard over the gland. The supraclavicular fossa was filled by the thyroid gland.

The lungs were clear, no râles were heard.

The right border of the heart at the second interspace was 5 cm from the midline, that at the third interspace, 6.5 cm, and that at the fourth interspace, 7 cm. The left border of the heart at the second interspace was 5 cm from the midline, that at the third interspace, 7 cm, that at the fourth interspace, 8.5 cm, and that at the fifth interspace, 10 cm.

The pulse was bounding, quick and regular in force and rhythm. The apex was heaving. No thrill was felt, and no murmur was heard.

The abdomen did not contain masses, and was not tender. The liver was not felt, the dulness extended 1 cm below the costal margin. The spleen was not felt.

The genitalia were normal.

The reflexes were equal and active. There were no disturbances of sensation.

*Laboratory Studies*—A blood count showed red cells, 3,320,000, hemoglobin, 60 per cent, white cells, 7,610. A differential count showed polymorphonuclear neutrophils, 73 per cent, polymorphonuclear eosinophils, 1 per cent, small monocytes, 11 per cent, large monocytes and transitionals, 14 per cent, unclassified cells, 1 per cent.

There was slight anisocytosis, the platelets looked normal

Examination of the stool gave negative results

The urine had a specific gravity of 1018, the reaction was acid, it contained albumin (+), but no sugar Microscopic examination showed a few white blood cells

On December 1, a teleoroentgenogram showed that the right border of the heart was 6 cm from the midline, and the left border, 8.5 cm

Roentgen examination of the chest did not show evidence of a substernal thyroid The lungs were clear except for a nontuberculous infiltration at the base of the right lung The heart was a trifle enlarged, particularly the second curve to the left<sup>2</sup>



Fig 1—Diffuse goiter with hyperthyroidism, before operation

*Treatment and Course*—December 2 The basal metabolic rate was +59 (poor test) The temperature was 101.8 F (rectal), the weight was 110 pounds (49.9 Kg)

A gynergen (ergotamine) test caused no subjective discomfort

An electrocardiogram showed a rate of 110 and a P-R interval of 0.16 second The mechanism was normal

Digitalis, 0.9 Gm, was given in one day Then 0.2 Gm was given once a day for fourteen days

December 5 Compound solution of iodine, 30 minims (19 cc), was given on this day and every day afterward for twelve days

December 11 A blood count showed 4,450,000 red cells and 78 per cent hemoglobin

<sup>2</sup> Parkinson, J., and Cookson, H The Size and Shape of the Heart in Goitre, *Quart J Med* 24:499 (July) 1931

December 15 The basal metabolic rate was +41 per cent (poor test) The temperature was 99 F (rectal), the weight was 127 pounds (57.6 Kg)

December 17 Digitalis and compound solution of iodine were discontinued Ergotamine, 0.5 mg, was given twice daily for two days without effect

December 19 Compound solution of iodine, 30 minims, was given on this day and every day afterward for nine days, without a change in the pulse rate (120)

December 28 Subtotal thyroidectomy was performed The gland was hard and slightly irregular, but was rather vascular

The pathologic examination revealed changes characteristic of exophthalmic goiter

The patient had a severe postoperative reaction, with a temperature of 105 F and a pulse rate of 184 for two days, after which the temperature and pulse rate

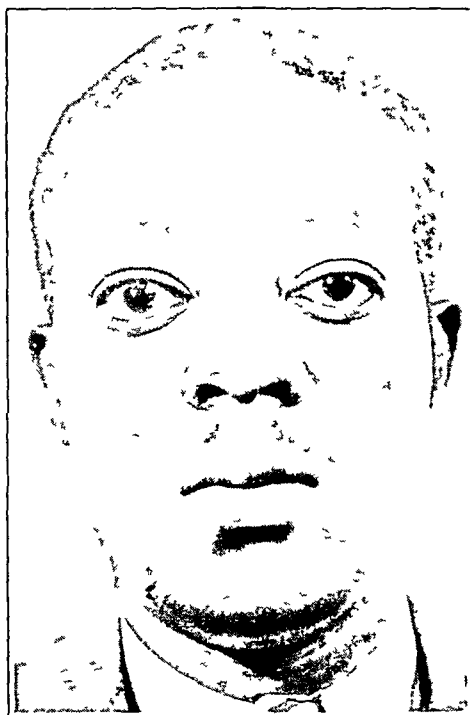


Fig 2—Two years after subtotal thyroidectomy

gradually fell in five days to normal, for the first time during the patient's stay in the hospital

Jan 15, 1927 The basal metabolic rate was -3 per cent The weight was 136 pounds (61.7 Kg)

January 16 The patient was discharged from the hospital improved

Following discharge from the hospital, the patient moved to Chicago and was not seen again until Feb 15, 1929

*Interval History*—After leaving the hospital in 1927, the patient lived for several weeks in Baltimore and for a few months in New York City then he went to Chicago He had not worked Eight months after leaving the hospital he began to notice that whereas his ankles had theretofore been a little swollen at night, they were staying swollen constantly and were enlarging About the same time he noticed that the ends of his fingers were enlarging and becoming curved, although they were not painful The swelling of his fingers and ankles progressed slowly until at the time of the second examination it involved the wrists and extended

from the ankles to the knees, leaving the feet unaffected. The only treatment had been rubbing with alcohol. The patient complained of no other symptoms, except that his eyes bothered him occasionally when he read. There had been no pain except on vigorous movement of the hands and legs; this pain had, however, been the cause of his not working. He had gained about 30 pounds (13.6 Kg.) in six months after leaving the hospital, but had lost weight since then.

*Second Examination*—Physical examination, which was made by me, showed that the patient was well nourished.

The skin was dry. The palms were slightly moist, the axillae were quite moist. The hair was normal in texture, there was a slight thinning over the crown.

The patient had marked bilateral exophthalmos. The upper lids were slightly swollen. Convergence was poor.



Fig. 3—Clubbed fingers, with swelling of the soft parts symmetrically distributed in the two hands.

The tick of a watch was heard normally. The tongue was broad and flat, and was moist. The teeth were in good condition. The tonsils were not enlarged.

The trachea was in the midline, the thyroid was not palpable, there was a well healed thyroidectomy scar.

There was no general glandular enlargement.

The lungs were clear to percussion and auscultation.

The pulses were equal and synchronous, and were regular in force and rhythm. The rate was 60 per minute.

The heart sounds were clear at the apex and the base. The second aortic sound was loud and "plupping." The blood pressure was 150 systolic and 110 diastolic.

The liver and spleen were not felt. There were no masses in the abdomen.

The phallus and gonads were normal. There was a slight left varicocele. The inguinal glands were slightly larger than normal.

The reflexes were very active. Chvostek's and Trousseau's signs were negative.

There was an extreme degree of clubbed fingers, with enlargement of the hands and wrists. There were a thickening and bowing of the left second metacarpal and



also a thickening of the soft parts around all of the middle phalanges. There was thickening of the wrists. The elbows and shoulders were normal. The feet were approximately normal. There was excessive edema from the top of low shoes to the knees. The skin of this area was brawny and pigmented.

*Impression*—The patient probably had slight postoperative myxedema. The interesting feature was the hypertrophic osteo-arthritis, a possible explanation of which may be found in the alteration of the circulation following a sudden reduction of the metabolic rate.

*Laboratory Studies*—The urine was a clear, medium amber, the specific gravity was 1.027, it was acid, it contained no sugar, a trace of albumin, a few hyaline casts, a few epithelial cells and white blood cells, but no red blood cells.



Fig 4—Brawny edema of the legs

A blood count showed hemoglobin, 91 per cent, red cells, 4,720,000, white cells, 13,650. A differential count showed polymorphonuclears, 73 per cent, polymorphonuclear eosinophils, 4 per cent, polymorphonuclear basophils, 1 per cent, small lymphocytes, 20 per cent, large lymphocytes, 2 per cent.

Röntgen examination showed that the lungs were clear. The heart and aorta were normal in size. The right border of the heart was 5 cm from the midline, the left border, 9.5 cm.

The metacarpal bones were short. There were a few periosteal changes in the bones of the hands and the legs, otherwise, the bones were normal.

On Feb 15, 1929, the basal metabolic rate was  $-9$  per cent (perfect test). The patient weighed 177 pounds, (80.3 Kg), the pulse rate was 56.

An electrocardiogram showed a rate of 52, the rhythm was sino-auricular, the P-R interval was 0.19 second. The T waves were all upright. There were normal sinus rhythm and sinus bradycardia.

On February 18, chemical analysis of the blood showed nonprotein nitrogen, 32 mg per hundred cubic centimeters, calcium, 11.4 mg, and phosphorus, 4 mg.

The patient was requested to enter the hospital for observation and treatment but declined and disappeared from sight until April 9, 1931.

*Interval History*—Since the patient was last seen he had worked spasmodically as a tailor's helper, but had not felt well. He had noticed no change in the size or shape of his hands and legs. In January, 1931, he fell, injuring his back and right leg, and he was still shaky and nervous from the fall, and had pain in the left flank.

On April 9, roentgen examination showed marked new bone formation in the bones of the hands and feet.

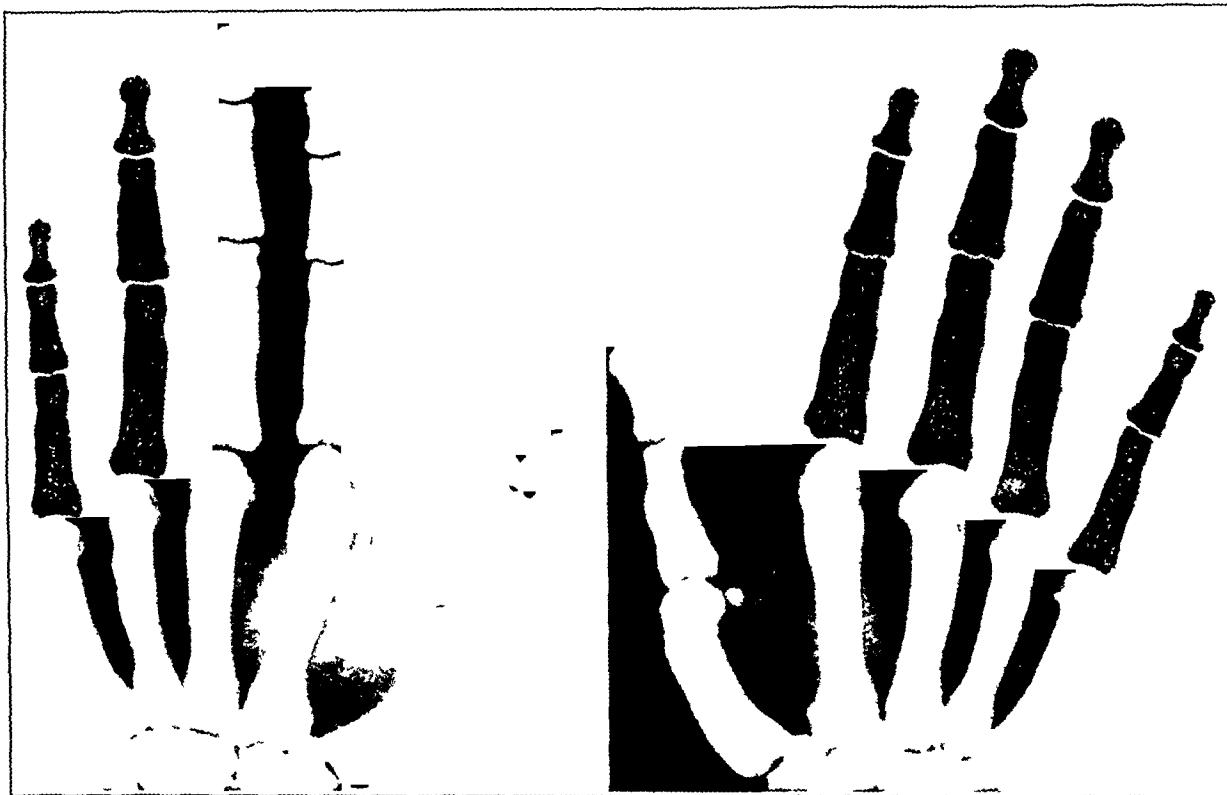


Fig 5—Roentgenogram taken two years after subtotal thyroidectomy, showing tufting of the terminal phalanges and marked subperiosteal new bone formation symmetrically distributed in the two hands and underlying the soft tissue swelling seen in the photograph.

On April 14, roentgen examination showed marked periosteal changes in the bones of the hands. The long bones, the head and the spine were normal.

The Wassermann reaction was negative.

The blood pressure was 160 systolic and 120 diastolic. It was the same in the two arms.

*Laboratory Studies*—Urinalysis showed a specific gravity of 1.016 for the specimen taken in the morning and 1.026 for the specimen taken in the afternoon, both specimens contained albumin (+) but no sugar. Microscopic examination revealed a few white blood cells and 1 hyaline cast.

The phthalein test gave the following reactions: first hour, 43 per cent, second hour, 12 per cent, totalling 55 per cent. Nonprotein nitrogen was 38 mg per hundred

cubic centimeters, total proteins, 7.95 mg, A/G ratio, 63/37, calcium, 10.2 mg per hundred cubic centimeters, phosphorus, 3.7 mg, and cholesterol, 230 mg

On April 24, the basal metabolic rate was —20 per cent (perfect test) The pulse rate was 54, the weight was 187 pounds (84.8 Kg)

On this day, thyroid medication was begun, 1 grain (0.065 Gm) a day After eighteen days the patient reported that he felt much better He had no pain in the back, and the pulse rate was 62 Thyroid extract, 2 grains (0.13 Gm) a day after fourteen days produced "quivers around the heart"

The capillaries of the nail beds were examined microscopically by Dr J Evans, who found an unusual condition There was a great dilatation of the venous side



Fig 6—Roentgenogram taken four years after subtotal thyroidectomy, showing increase in bony changes

of the capillaries, and the arterial side showed an extreme degree of tortuosity The capillary pressure was slightly elevated<sup>3</sup>

Thyroid extract, 1½ grams (0.097 Gm) a day for a month, produced very little change, and the patient was annoyed by insomnia, aching around his eyes and great fatigue in the afternoon which required two hours of sleep

The patient took thyroid steadily from Nov 22, 1931, to two weeks before this article was written He felt somewhat better, but there was no noticeable change in the condition of his hands and legs

<sup>3</sup> Holger F Ueber Akropachie (Trommelschlagelfinger und Osteoarthropathie), Wien Arch f inn Med 1 35, 1920 Holger said "Interesting but inconclusive is the finding of normal capillaries in clubbed fingers in vivo in one case"

*Summary of Case*—A young colored man of 22 years was admitted to the hospital in November, 1926, suffering from a rather severe form of diffuse goiter with hyperthyroidism, which, judging from the history, had existed for two years. Following the usual treatment and operation the basal metabolic rate fell from the admission

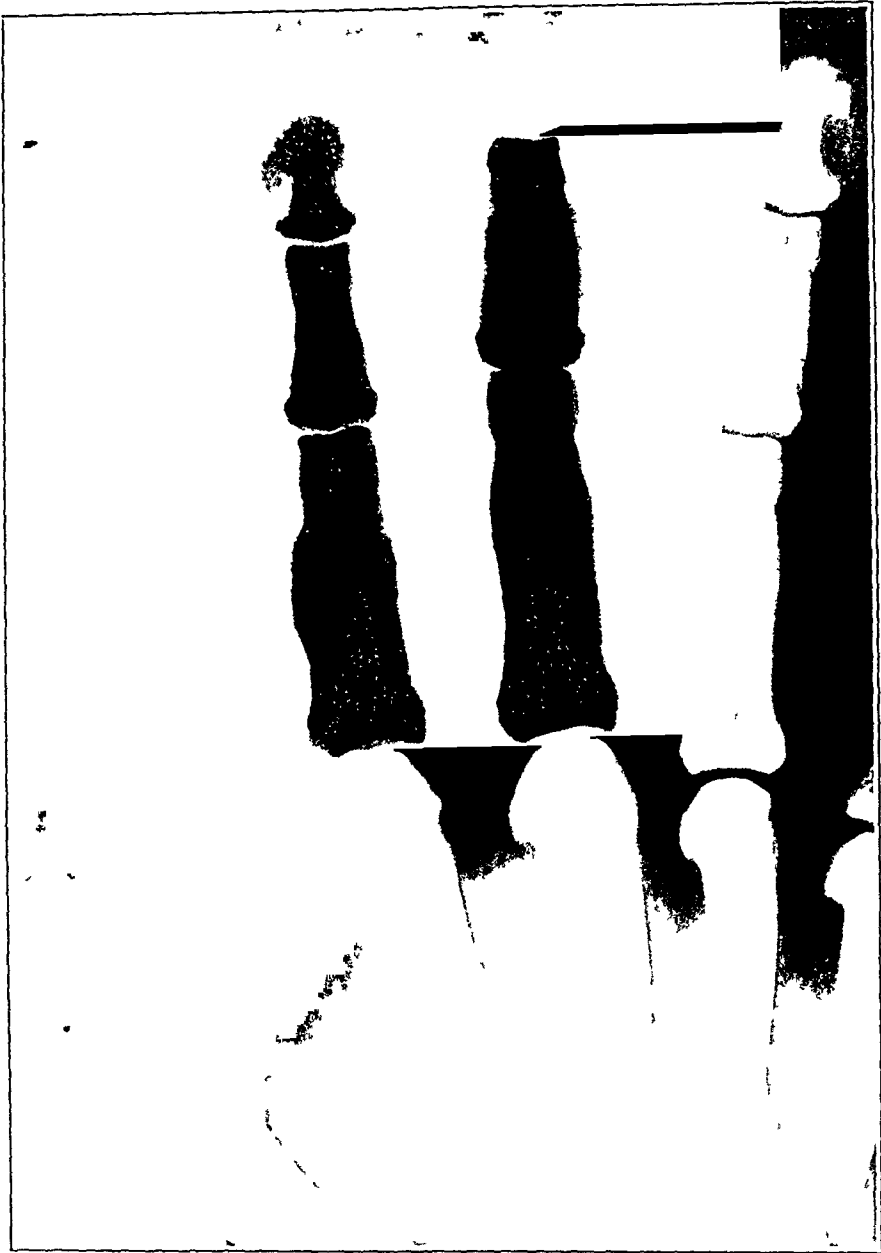


Fig 7—Larger view of roentgenogram taken four years after subtotal thyroidectomy

level of 59 per cent above normal to 3 per cent below normal, and he gained 26 pounds (11.8 Kg). After his discharge from the hospital he gained about 30 pounds (13.6 Kg) more in eight months. At the end of this time he noticed clubbing of the fingers and a change in the swelling of his ankles which, previously transitory, had become constant



Fig 8—Roentgenogram of skull, showing a normal sella turcica and absence of characteristic changes seen in Paget's disease

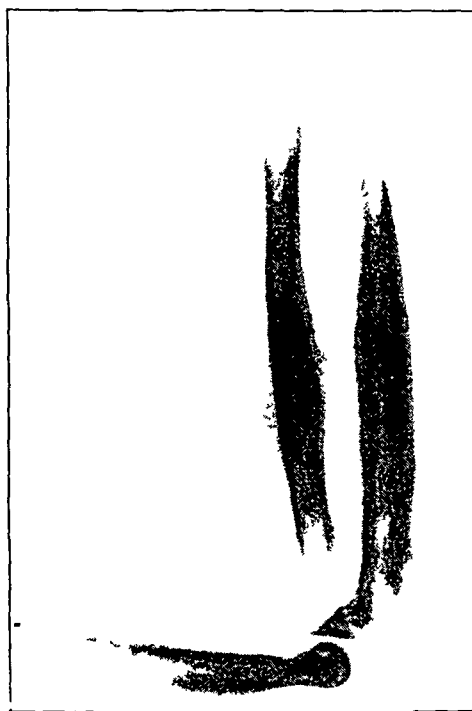


Fig 9—New bone formation in long bones of the arms, most marked in the middle of the diaphysis

and firmer. The conditions increased gradually, but with only slight pain and that only on vigorous movement of the hands. In 1929, the basal metabolic rate was  $-9$  per cent, and x-ray pictures showed laying down of new bone under the periosteum of the bones of the hands and feet and the long bones of the extremities. In April, 1931, the basal metabolic rate was  $-20$  per cent and the new bone formation had become more extensive. A diagnosis of postoperative hypothyroidism with secondary hypertrophic osteo-arthritis was made, and thyroid replacement therapy was instituted, with definite improvement in the subjective symptoms. No convincing change has been noted in the bones since the patient began to take thyroid, although an apparent thinning of the subperiosteal new bone has been seen at the end of three and a half months.

#### COMMENT

This is the first reported case of clubbed fingers with subperiosteal new bone formation occurring in association with disease of the thyroid gland. The changes in the bones of the hands are as extensive as any described in the literature, and the swelling of the legs is greater. The new bone is confined to portions of the skeleton which are covered by periosteum and is not seen in the joints. It is greatest in the mid-portion of the short bones, but involves the entire length of most of the long bones as well. There is also a well marked increase in the tufting of the terminal phalanges of the fingers. Because the swelling of the soft parts in this case occurs so clearly above the bony changes, even including the tufting of the terminal phalanges, it would seem probable that the clubbed fingers which are seen in this condition may represent a soft tissue change different from that of clubbed fingers which occur without any underlying bony change.

Most patients acquire the new bone in thin layers under the periosteum, several layers becoming visible in the x-ray film as time goes on. The case reported, however, shows a piling up of new bone with a fuzzy surface to a thickness of 2 or even 3 mm. This difference might well be due to the rapidity of the process. The swelling of the soft parts in the hand (and presumably elsewhere also) occurs over the bony swelling as though it were part of the same process. One extraordinary feature of the condition, which has been commented on before (Fraenkel<sup>4</sup>), is the symmetry of the process. The same portion of the same bones in the two hands is involved to approximately the same degree. Hitherto this condition has been described as being secondary to suppurative intrathoracic lesions, mediastinal new growths, tumors of the lung, abscess of the liver, pyelonephritis, cirrhosis of the

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4 Fraenkel, E. Ueber allgemeine Periostitis hyperplastica (Osteo-arthropathie hypertrophante pneumique), *Fortschr a d geb d Rontgenstrahlen* 25 401, 1918.

liver with jaundice, certain obstructive lesions of the gastro-intestinal tract, possibly syphilis, and, perhaps incorrectly, congenital heart disease. The case reported presents none of these features.

In 1889, von Bamberger<sup>5</sup> reported two cases of bronchiectasis in which clubbing of the fingers and toes and gross changes in the bones of the lower legs developed. He attempted to reproduce the bony changes in rabbits by injecting the patient's sputum into the animals, on the theory that the etiologic factor was a toxin liberated by the suppurative process.

The following year Pierre Marie<sup>6</sup> described a syndrome which he called hypertrophic pulmonary osteo-arthritis (ostéo-arthropathie hypertrophiante pneumique), consisting of widespread enlargement of the bones and clubbing of the fingers in cases of cardiac and pulmonary disease. He was careful to differentiate this condition from acromegaly, although his best case, seen in the light of further knowledge, undoubtedly combined certain features of acromegaly with hypertrophic pulmonary osteo-arthritis. Later on much interest was aroused by the constant accompaniment of clubbed fingers (Trommelschlagelfingern) with the bony changes, as this secondary enlargement of the distal phalanges of the fingers and toes had been noted by Hippocrates. Trousseau,<sup>7</sup> after several centuries during which it had been overlooked, described the condition of clubbed fingers accurately and pointed out its association with advanced pulmonary tuberculosis, empyema, emphysema, nervous asthma and organic heart disease.

After the appearance of von Bamberger's article in Germany and Marie's in France, clinicians in many countries reported cases secondary to various diseases, among which were tuberculosis, bronchiectasis, empyema, abscess of the lungs, tumor of the lungs, lymphoblastoma, organic heart disease, syphilis, cirrhosis of the liver with jaundice and amebic hepatitis, with a few apparently spontaneous cases. In 1898, Schmidt<sup>8</sup> collected the literature on the subject. He concluded that clubbed fingers, with the change confined to the soft tissues, represent an early stage of what may or may not further develop into the more advanced and rarer form with bony thickening. He thought that the joints are never involved, and that the greatest swelling occurs in the middle portion of the shaft of the long bones. Most of the bones of the skeleton may show changes, including the clavicle and the ilium.

5 von Bamberger, E. Bronchiektasie, *Wien klin Wchnschr* 2 226, 1889.

6 Marie, Pierre. De l'ostéo-arthropathie hypertrophiante pneumique, *Rev de méd* 10 1, 1890.

7 Trousseau, Armand. Lectures on Clinical Medicine, translated by John Rose Cormack, Philadelphia, Lindsay & Blakiston, 1868, vol 3.

8 Schmidt, M. B. Die allgemeine hyperplastische Periostitis und Ostitis, *Ergebn d allg Path u path Anat* 5 932, 1898.

In this country, Thayer,<sup>9</sup> Janeway,<sup>10</sup> Landis<sup>11</sup> and others have written on the subject, and in 1915, Locke<sup>12</sup> summarized the literature and added five carefully studied cases. He considered the clubbed fingers and bony swelling as part of the same condition and stated that early subperiosteal changes could be demonstrated in all of his cases of clubbed fingers.

In 1917, Fraenkel<sup>4</sup> reported seven additional cases and argued against the earlier impression (agreeing on this point with Schmidt) that the joints and periarticular tissues (cartilage) are commonly involved. None of the cases he studied at autopsy showed any such change, and he conceived the condition to be a form of hyperplastic periostitis which involves characteristically the midbones of the hands and feet and the midportion of the long bones. The underlying old bone may be unchanged or may show thickening or thinning.

A splendid article on the subject was published in 1920 by Hogler,<sup>5</sup> from Falta's Clinic in Vienna. He reported five cases, one of which was merely a case of clubbing of the fingers, and he carefully analyzed the case reports from the previous literature. If his conclusions are correct, and it certainly seems that in most respects his points are well taken, some of the ideas on the subject must be readjusted.

In an effort to eliminate the obvious disadvantages of most of the names that have been applied to this condition, such as chronic hypertrophic pulmonary osteo-arthropathy, hyperplastic periostitis, ossifying periostitis, secondary ossifying periostitis, toxic periostitis and toxicogenic osteoperiostitis ossificans, Hogler suggested the name acropachy. By this name he avoided pathologic descriptive terms, which are likely to be incorrect (there is no evidence of inflammation of the periosteum, and the joints are rarely involved), and terms suggesting the etiology, which are also likely to be incorrect or inconclusive, and he hinted at a similarity to acromegaly, with which the condition was first confused.

The change in the bone consists of a deposition of new bone between the cortex and the periosteum of the long bones, particularly the lower ends of the bones of the forearms and the lower legs and the metacarpal and metatarsal bones. In extreme cases similar changes have been described in the clavicles, ribs, pelvic bones, scapulae and malai bones, and even in the transverse processes of the vertebrae. The joints are

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<sup>9</sup> Thayer, W. S. Hypertrophic Pulmonary Osteo-Arthropathy and Akromegaly, Philadelphia M. J. **2** 955, 1898.

<sup>10</sup> Janeway, T. C. Hypertrophic Osteo-Arthropathy. With Report of Two Cases, Am. J. M. Sc. **126** 563, 1903.

<sup>11</sup> Landis, H. R. M. Hypertrophic Pulmonary Osteoarthropathy with a Report of Two Cases, Pennsylvania M. J. **10** 852, 1907.

<sup>12</sup> Locke, E. A. Secondary Hypertrophic Osteo-Arthropathy and Its Relation to Simple Club-Fingers, Arch. Int. Med. **15** 659 (May) 1915.



never involved in the original process, although involvement of the end of the bone may lead to disability in the joint. The underlying bone shows no change except that seen following disuse. Histologically, the cortical part of the bone is little if any changed (Schlagenhauser<sup>13</sup>). Hogler disagreed with Sternberg, who described evidence of inflammation in the periosteum itself. More and more, he said, it looks like a hyperplastic process of the periosteum. This has a true analog in the osteophyte building during pregnancy, but is not a true inflammation.

Often there is swelling of the wrists and ankles, and the swelling of the ankles may even amount to brawny edema.

The condition may be painful or associated with tender points over the affected areas.

Although acropachy usually occurs in patients with clubbed fingers several cases have been described in which clubbed fingers were not present, and also innumerable cases of clubbed fingers have occurred without any bony changes. For these reasons it appears that this syndrome is quite distinct from that of clubbed fingers, although the two conditions probably are caused by the same variety of underlying morbid process.

On careful analysis, most of the authentic cases were found to occur in patients suffering from some collection of pus in the chest or some form of mediastinal new growth, usually lymphogranuloma. Hogler doubted whether any true case has occurred secondary to congenital heart disease without accompanying pulmonary disease. Unilateral involvement of one arm has been described in cases of aneurysm of the subclavian artery and in trauma to the brachial plexus. A number of characteristic cases have been observed following biliary cirrhosis of the liver with jaundice. Finally, a small number of cases with no obvious etiology may be found in the literature.

Hogler thinks it interesting that most cases follow a purulent process in the thoracic cavity or a mediastinal growth from which some toxic substance may emanate. In one of the cases of lymphogranuloma with a mass in the mediastinum which he reported, the patient was treated by irradiation of the mediastinal mass. Along with the general clinical improvement, the bony changes, which had been extreme, faded away until they were hardly noticeable in the x-ray films. Hogler pointed out that Gerhardt,<sup>14</sup> Liebermann,<sup>15</sup> Ruhle<sup>15</sup> and Hoffmann<sup>16</sup>

13 Schlagenhauser, F. Ueber diffuse ossifizierende Periostitis, *Ztschr f Heilk* 25 364, 1904.

14 Gerhardt, Carl. *Lehrbuch der Auskultation und Percussion*, Tubingen, H. Laupp, 1900, p. 26.

15 Liebermann, cited by Hogler.<sup>3</sup>

16 Hoffmann, V. Ein Beitrag zur Kenntnis der Osteo-arthropathie hypertrophante pneumique, *Deutsches Arch f klin Med* 130 201, 1919.

wished to give chief etiologic importance to congestion, but he said later that congestion plays no important rôle, since cases of heart failure are no longer included as a special group, and since there is another group of cases of high grade acropachy in which stasis in the large and small circulation is entirely precluded<sup>17</sup> After considering the possible influence of toxins on trophic nerves in the periosteum, the possibility of an irritating substance which perhaps can be generated by malignant tumors, etc., Hogler finally concluded that it must be admitted that this hypothesis really is nothing but another way of writing down the important facts which depend on various observations and experimental data

In 1923, Schirmer<sup>18</sup> published an autopsy report on one of Hogler's patients who subsequently died of "lymphoblastoma" or Hodgkin's disease There existed infantilism with a normally formed but extremely underdeveloped thyroid gland and with a normal hypophysis He referred to Franchini,<sup>19</sup> who in 1910 reported a case of putrid bronchitis with atrophy of all the endocrine glands and an infantile habitus Braun<sup>20</sup> found an adenoma or some other lesion of the hypophysis in three or four cases of this condition, and suggested that the bony changes are caused by a dysfunction of the pituitary gland

The case reported in this article presents several interesting features In the first place, it developed shortly after the condition had changed quite suddenly from a condition of hyperthyroidism to one of hypothyroidism by iodine medication followed by subtotal thyroidectomy Careful search before operation and on many occasions after operation over a period of five years, has failed to reveal any other disease process either in the thoracic cavity or elsewhere in the body One is forced, then, to conclude that in this case the changes were in some way produced by a rapid alteration in the patient's endocrine balance No such changes have been observed in exophthalmic goiter or in myxedema Long-standing cases of hyperthyroidism do exhibit generalized osteoporosis, and conversely myxedema tends to produce a widespread increased density of the bone, but without change in the size of the bone and without new bone formation The changes of the bones in parathyroid disease are striking, but, again, they differ mark-

17 I should like to suggest that a slowing of the entire blood flow may occur without local evidence of congestion and yet still have its effect on such tissues as the periosteum, even if the generally accepted connection between congenital heart disease and acropachy is incorrect

18 Schirmer, Oskar Beitrag zur Kenntnis der Akropachie (Osteoarthropathie hypertrophante pneumique), Wien Arch f inn Med 5 345, 1923

19 Franchini, G Sull'osteopatia ipertrofica pneumica di Marie Studio clinico de anatomo-pathologico, Riv crit di clin med 11 745, 1910

20 Braun, H Ueber Trommelschlagelfinger, Med Klin 14 1, 1918

edly from those in the case presented by involving the original bony structure in a condition known as osteitis fibrosa cystica. No indication of parathyroid dysfunction in my case could be brought to light, and the determinations of the blood calcium and phosphorus were always normal. That one or more of the other glands of internal secretion were altered functionally by the operation on the thyroid gland seems likely, but I am unable to connect such changes with the development of new bone. The thymus gland is frequently found enlarged in cases of exophthalmic goiter. That the thymus should assume such proportions as to be considered a mediastinal tumor which might produce pressure and yet not be visible in the x-ray picture of the chest seems doubtful, but barely possible. Pressure symptoms in an adult from an enlarged thymus are rarely if ever seen. No involvement of the pituitary gland was demonstrable by roentgen examination of the sella turcica, by determination of the visual fields or by sugar tolerance tests. It is inferred that a change in the functions of the pituitary gland probably accompanies changes in the function of the thyroid gland, but in the case reported a skeletal deformity quite different from acromegaly or gigantism was encountered.

In the roentgenograms of the pelvic bones certain areas of rarefaction faintly suggested Paget's disease, but examination of the other bones, particularly the skull and the spine, did not support this idea, and changes like those seen in the bones of the hands in my case have not been described in Paget's disease.

One might quite properly, it seems to me, place some importance on the sudden change in blood flow which is known to take place in any case when a hyperthyroid condition is abruptly converted into one of hypothyroidism. Blumgart<sup>21</sup> and others have shown that in hyperthyroidism the blood volume is greater than normal, the minute output of the heart is more than normal, and the blood flow is faster than normal. They have also shown that in hypothyroidism the blood volume, the minute output of the heart and the rate of blood flow are reduced below normal. It would appear, then, that in a young adult this sudden slowing of the circulation has for some reason been accompanied by the remarkable abnormality described. The perfect bilateral symmetry of the lesion requires an explanation. What condition, one must ask oneself, might affect the bone or periosteum of the two arms in such an irregular but identical manner? Would not a circulating toxin call forth a similar response in all of the proximal phalangeal bones instead of selecting the mesial surface of each proximal phalangeal bone on

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21 Blumgart, H. L., Gargill, S. L., and Gilligan, D. R. Studies on the Velocity of Blood Flow. XIII. The Circulatory Response to Thyrotoxicosis, *J. Clin. Investigation* 9: 69, 1930, XIV. The Circulation in Myxedema with a Comparison of Blood Flow in Myxedema and Thyrotoxicosis, *ibid.* 9: 91, 1930.

which to concentrate its attentions? Alteration of the circulation, on the other hand, might easily affect one finger, for instance, the index finger, before the others, and this, of course, would be true for both sides alike. In my case, as in those reported by Hogler, a persistent, edema-like swelling of the lower extremities is strong evidence in favor of local congestion. One is led to wonder whether the common factor in all of these cases may not be some change in the circulation. Such a change occurs in cases of jaundice with bradycardia and might also occur if a fraction of the lung substance ceased to act properly in its function of aerating the blood. Mechanical pressure from a mediastinal mass does interfere with the blood flow in the great vessels, and the disappearance of the bone changes in such a case following deep roentgen therapy to the mediastinum may be accounted for by the removal of such pressure. It would seem that the circulatory change must be abrupt, and that its effect is most striking when it occurs in patients whose osseous system is still in the process of adolescent growth.

It is important to point out the obvious objections to considering circulating toxins the cause of acropachy. Why, for instance, should an abscess of the lungs produce such a toxin and abscesses elsewhere in the body not produce it? Why should it occur in its most advanced form with Hodgkin's disease which involves the glands of the mediastinum, and not occur with Hodgkin's disease confined to glands elsewhere in the body? Why should it occur with carcinoma of the bronchus and not with carcinoma in other parts of the body? Why should this toxin be liberated by pulmonary tuberculosis and not by tuberculosis of other organs?

As may be inferred, I am not in favor of the theory of a circulating toxin. In all honesty, however, I must confess self-evident objections to the theory of an altered blood flow. Why does one not see acropachy in the many cases of unilateral femoral thrombophlebitis? So far as I know, subperiosteal new bone may occur in these cases without ever having been noticed. If an insufficient oxygen supply is an important feature, why has acropachy not been found in long-standing cases of severe anemia? It may be, I think, that the tissue adjustment to anemia is gradual, whereas in acropachy time for adjustment is lacking.

#### SUMMARY

I have presented the case of a young colored man in whom diffuse goiter with hyperthyroidism developed for which subtotal thyroidectomy was performed. Eight months later he noticed clubbing of the fingers and brawny swelling of the legs, and when examined two years later was found to have an extreme degree of acropachy. A careful exami-

nation made at the time of operation and repeated on two further occasions, two and again four years after operation, failed to reveal other disease or lesion of the heart or lungs. I found no mention of similar cases in the literature, but I have discussed the important articles on acropachy as it occurs in various other conditions. Nothing is known concerning the mechanism of the bony change in this syndrome.

The new and unusual case I have reported adds strong evidence of the importance of altered blood flow in the production of subperiosteal new bone formation. The only conclusion I am able to reach, after contemplating the many factors involved in cases of acropachy, is that an altered blood flow offers itself as the most plausible common etiologic factor.

# RELATIONSHIP BETWEEN OXYGEN CONSUMPTION AND NITROGEN METABOLISM

## II IN LEUKEMIA

C W BALDRIDGE, M D

AND

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IOWA CITY

In a previous communication<sup>1</sup> we presented evidence of a decrease in the total oxygen consumption during induced remissions in pernicious anemia. A relationship between the oxygen consumption and nitrogenous metabolism was discussed. The data in the present report were obtained by metabolic studies in leukemia, another disease group in which there is an altered rate of oxygen consumption without a recognized disturbance in thyroid function. We again wish to stress the relationship between oxygen consumption and nitrogenous metabolism.

The published reports of metabolic studies in leukemia contain much important information, but the established facts have not been satisfactorily correlated. We do not propose to present an exhaustive review of the literature but rather to mention only those observations which bear directly on our present problems.

## REVIEW OF LITERATURE

It is quite universally agreed that the rate of oxygen consumption is increased, sometime during the course, in all forms of leukemia. Grafe,<sup>2</sup> though not the first<sup>3</sup> to observe the increased basal metabolic rate in leukemia, has been the most persistent contributor to the literature on the subject and has advanced many of the prevalent theories.

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1 Baldrige, C W, and Barer, A. Studies on the Relationship Between Oxygen Consumption and Nitrogen Metabolism. I. In Pernicious Anemia, *J Clin Investigation* **10** 529, 1931.

2 (a) Grafe, E. Die pathologische Physiologie des Gesamtstoff- und Kraftwechsels bei der Ernährung des Menschen, *Ergebn d Physiol* **21** 464, 1923. (b) Die Steigerung des Stoffwechsels bei chronischer Leukämie und ihre Ursachen, *Deutsches Arch f klin Med* **102** 406, 1911, (c) Stoffwechseluntersuchungen bei Milz- und Lebererkrankungen, *Deutsches Arch f klin Med* **139** 354, 1922, (d) *Handbuch der normalen und pathologischen Physiologie*, Berlin, Julius Springer, 1928, vol 5, p 267.

3 Bohland, K. Ueber den respiratorischen Gaswechsel bei verschiedenen Formen der Anämie, *Berl klin Wchnschr* **30** 417, 1893.

as to the genesis of the increased utilization of oxygen in this disease. It has been suggested that the oxygen consumption in afebrile leukemia, which is often 50 per cent above the normal and may reach 100 per cent above, can be explained as follows: (1) increased pulse and respiratory rates, (2) increased utilization of oxygen by extra leukocytes, especially the abundant and very active young forms, both in the blood and in the tissues, (3) increased activity and extent of the hematopoietic tissue, (4) anemia (in which an increased amount of oxygen is used by young erythrocytes), and (5) possibly toxic factors.

The possibility that the spleen has an endocrine function and thus plays a rôle in general metabolism has been suggested by the Asher school. Since both the spleen and the metabolism are abnormal in leukemia, suggestions as to a cause and effect relationship have naturally appeared in the literature. The discussions, which have been summarized by Stuber,<sup>4</sup> are very vague and unconvincing. Stuber also takes the unique position of attributing part of the increased metabolism in leukemia to an increased imperceptible loss of water.

Murphy, Means and Aub<sup>5</sup> found that direct and indirect calorimetry agreed in a case of lymphatic leukemia, thus showing that no measurable heat was derived from permanently anaerobic reactions. Isaacs<sup>6</sup> suggested that nuclear destruction might be related to the increased oxygen consumption in blood dyscrasias because of the increased uric acid excretion, which is common to pernicious anemia, leukemia and polycythemia vera. Riddle and Sturgis<sup>7</sup> as well as Krantz and Riddle<sup>8</sup> found an occasional rise in oxygen consumption after roentgen therapy, and suggested the possibility that blood destruction might also play a rôle in increasing the oxygen consumption in leukemia. Both groups of workers appear to have been more impressed, as Gunderson<sup>9</sup> had been, with a fairly good correlation between the number of circulating immature cells and the total metabolism.

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4 Stuber, K. Ueber den Gaswechsel und die spezifisch-dynamische Eiweisswirkung bei Leukämien und Pseudoleukämien, *Ztschr f klin Med* **111** 214, 1929.

5 Murphy, J. B., Means, J. H., and Aub, J. C. The Effect of Roentgen-Ray and Radium Therapy on the Metabolism of a Patient with Lymphatic Leukemia, *Arch Int Med* **19** 890 (May) 1917.

6 Isaacs, R. Pathologic Physiology of Polycythemia Vera, *Arch Int Med* **31** 289 (Feb) 1923.

7 Riddle, M. C., and Sturgis, C. C. Basal Metabolism in Chronic Myelogenous Leukemia, *Arch Int Med* **39** 255 (Feb) 1927.

8 Krantz, C. I., and Riddle, M. C. The Basal Metabolism in Chronic Lymphatic Leukemia, *Am J M Sc* **175** 229, 1928.

9 Gunderson, A. H. The Basal Metabolism in Myelogenous Leukemia and Its Relation to the Blood Findings, *Boston M & S J* **185** 785, 1921.

A considerable amount of information has accumulated from experimental work bearing directly or indirectly on the various factors which have been thought to contribute to the increased gaseous metabolism in leukemia. We believe that a critical review of these factors in an attempt to evaluate their importance would be worth while even though it is readily admitted that in vitro experiments of the Warburg type may not give exact information as to gaseous metabolism in vivo.

#### THE INFLUENCE OF CARDIAC AND RESPIRATORY RATES

It is well known that the pulse rate usually increases as a *result* of increased oxygen consumption. It is also known that the rate of absorption of oxygen in the lungs is independent of the respiratory rate<sup>10</sup>. Changes in the cardiac and respiratory rates within reasonable limits, therefore, will influence the oxygen consumption only by virtue of changes in the muscular effort involved. Riddle and Sturgis<sup>7</sup> found that in myelogenous leukemia the pulse rate increased about 7 per cent for each 10 per cent increase in the basal metabolic rate. In our own patients with chronic leukemia the basal respiratory rate was rarely found to be above 18 per minute. Grafe has estimated that if both the cardiac and respiratory rates were doubled, the total metabolism would thereby be increased 8 per cent. However, we have never found either the cardiac or the respiratory rate to be doubled in patients with afebrile leukemia under basal conditions. Starling and Visscher<sup>11</sup> found that an increase in the heart rate of about 35 per cent caused an increase of about 20 per cent in the oxygen consumed by the heart-lung preparation when the diastolic volume of the heart was kept constant. The same investigators<sup>12</sup> also found that the oxygen consumption of the heart-lung preparation was about 5 per cent of the total for the anesthetized animal. It should be stated, however, that the actual oxygen consumption of the heart-lung preparation of Starling and Visscher was about 10 per cent of the calculated basal requirement for dogs weighing from 8 to 9 Kg. (This was the average weight of dogs used by these investigators). With the pulse rate changes observed by Riddle and Sturgis, it can be seen that in the average leukemic patient with a basal metabolic rate 50 per cent above normal there would be a 35 per cent increase in pulse rate. The amount of oxygen used by extra heart beats per se would therefore be approximately from 1 to 2

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10 Pfleger, E, quoted by Lusk, G. The Science of Nutrition, Philadelphia, W B Saunders Company, 1928, p 32

11 Starling, E H, and Visscher, M B. The Regulation of the Energy Output of the Heart, J Physiol 62 243, 1927

12 Visscher, M B. Personal communication



per cent of the total oxygen consumption if relationships in the dog can be transferred to man. The extra muscular effort occasioned by the slight increase in respiratory rate should be of even less significance.

#### THE INFLUENCE OF EXTRA LEUKOCYTES

An increase in the total leukocytes of the body might be expected to increase the basal metabolic rate since their presence would increase the surface area but slightly, and since they replace structures of relatively low metabolism such as fat, connective tissue, blood plasma and erythrocytes. All recent investigators agree, however, that there is no consistent or linear relationship between the number of extra leukocytes in the blood and the total oxygen consumption. We have made similar observations as well as an attempt to correlate the size of the spleen and liver with the height of metabolism but always with inconsistent results. Such a parallelism would be mandatory if the respiration of these added leukocytes were the principal cause of the increased metabolism in leukemia. Furthermore, the apparent correlation between the number of immature leukocytes and the total metabolism as suggested by Gunderson,<sup>9</sup> by Riddle and Sturgis<sup>7</sup> and by Krantz and Riddle<sup>8</sup> cannot be due directly to the respiration of these young cells. Glover, Daland and Schmitz<sup>13</sup> and Daland and Isaacs<sup>14</sup> concluded that young leukocytes consume less oxygen than adult cells of the same series, while Soffer and Wintrobe<sup>15</sup> concluded that if allowance were made for concentration the oxygen consumption of adult and young leukocytes would be about the same. There are no results to substantiate the claim of Grafe that "the active young forms" use more oxygen than adult leukocytes. Since the literature contains many studies on the oxygen consumption of leukemic blood, it is easy to calculate the amount of oxygen used by leukemic blood as contrasted with the normal. Considering that the blood constitutes 7 per cent of the body weight<sup>16</sup> and using an average of the results obtained by Glover, Daland and Schmitz for the respiration of leukemic blood, it appears that the blood of leukemic patients may use an average of 3 per cent of the normal total oxygen consumption. The gaseous metabolism of leukemic blood as determined by Glover, Daland and

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13 Glover, E. C., Daland, G. A., and Schmitz, H. L. The Metabolism of Normal and Leukemic Leukocytes, *Arch Int Med* **46** 46 (July) 1930

14 Daland, G. A., and Isaacs, R. Cell Respiration Studies, *J Exper Med* **46** 53, 1927

15 Soffer, L. J., and Wintrobe, M. M. The Metabolism of Leukocytes from Normal and Leukemic Blood, *J Clin Investigation* **11** 661, 1932

16 Chang, H. C., and Harrop, G. A., Jr. The Determination of the Circulating Blood Volume with Carbon Monoxide, *J Clin Investigation* **5** 393, 1928

Schmitz gave results of the same order of magnitude as those obtained by Daland and Isaacs,<sup>14</sup> by Hastings and Davis,<sup>17</sup> and by Barron and Harrop.<sup>18</sup> Grafe, in earlier work, obtained much higher figures from which he calculated that the blood might use as much as 10 per cent of the total oxygen consumed.<sup>2b</sup> Let us assume that the leukocytes which are extravascular but which are not involved in cell division or metaplasia (so-called infiltrated leukocytes) are twice as numerous and have the same respiratory activity as the circulating leukocytes. If the presence of such leukocytes did not affect the calculated surface area of the patient, it can be seen that they might use 6 per cent of the total normal oxygen consumption. This estimation is probably extremely generous since the *in vitro* oxygen consumption of leukocytes is much lower when they are grouped in large masses than when they are well diluted in plasma.<sup>19</sup>

#### INFLUENCE OF INCREASED EXTENT AND ACTIVITY OF THE HEMATOPOIETIC BONE MARROW

The extent of leukopoietic tissue in all types of leukemia is greatly increased both because of replacement of fat in the bone marrow and because of metaplasia outside the normal hematopoietic tissue. Metaplasia will be discussed with "activity," however, so that for the moment, we are concerned only with the extent of the bone marrow. In leukemia it is common to find the normal hematopoietic marrow of the flat bones more cellular than usual and in addition a partial or complete replacement of the fatty marrow of long bones by hematopoietic tissue. In addition to the increase in extent of the bone marrow, erythroblastic elements are often partially replaced by leukoblastic elements, which latter cells are usually considered to be more actively respiring than the former. However, it should be remembered that leukoblasts use no more or even less oxygen than leukocytes of the corresponding series, and that the possible capacity of the bone marrow is limited (from 1,600 to 4,000 cc).<sup>20</sup> No exhaustive studies as to the relative numbers of cells in the normal and in the leukemic bone marrow are available at present, but it is estimated by Isaacs<sup>21</sup> that the nucleated cells of the sternal marrow cannot be increased more than threefold. Let us guess for the present that there may be six times as many cells

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17 Hastings, A. B., and Davis, J. E. Personal communication.

18 Barron, E. S. G., and Harrop, G. A., Jr. *Studies on Cell Metabolism*. Metabolism of Leukocytes, *J. Biol. Chem.* **74**: 89, 1929.

19 Soffer and Wintrobe.<sup>15</sup> Hastings and Davis.<sup>17</sup> Barron and Harrop.<sup>18</sup>

20 Schilling, V. *Handbuch der normalen und pathologischen Physiologie*, Berlin, Julius Springer, 1928, vol. 6, part 2, p. 748.

21. Isaacs, R. Personal communication.

in the leukemic bone marrow as in the normal Breza<sup>22</sup> determined the metabolism of the bone marrow of rabbits and guinea-pigs by the Warburg technic. She calculated that the whole hematopoietic bone marrow used 1.5 per cent of the total oxygen consumed by the animals in basal condition, whereas the red bone marrow constituted 2 per cent of the body weight. The same investigator obtained a single reading on human bone marrow which was considerably higher but which needs confirmation. It is hard to understand how an increase in the amount of a tissue the oxygen consumption of which per unit of weight is below the average for the whole body could greatly increase total metabolism even though it replaced structures having a still lower respiratory rate. If the figures cited can be accepted as approximately correct, it becomes obvious that an increase in the extent of the bone marrow would be relatively unimportant in its influence on total oxygen consumption, especially if the oxygen consumption of bone marrow cells is inversely proportional to the concentration<sup>15</sup> as is the case in blood.

The effect on total metabolism of increased activity of blood-forming tissue must be approached from several different angles since the effect of this function alone as separate from other body functions has not been studied. It is essential that we first analyze the meaning of "activity of blood-forming tissue" so far as this is possible. Active hematopoiesis has not been demonstrated to involve any type of work comparable to that of a contracting muscle or a secreting gland. Activity seems to consist only in cell division so far as the true hematopoietic tissue is concerned. The activity of the reticulo-endothelial cells of the bone marrow in the disintegration of broken down erythrocytes is not especially abnormal in leukemia, as judged by the amount of ingested hemosiderin. Furthermore, the latter function has apparently not been considered by those who feel that activity of the bone marrow is an important cause for increased gaseous metabolism in leukemia. We may therefore turn our attention to the amount of energy consumed in cell division.

Loeb<sup>23</sup> showed that in obligatory aerobic eggs, cell division stopped when oxygen was removed from the system. This finding led Zuntz, Liebig, Pflüger and others to suppose that potential energy was stored during growth. However, Warburg<sup>24</sup> was able to show that cell

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22 Breza, J. Studien über Knochenmarksatmung, *Arch. f. exper. Path. u. Pharmacol.* **117** 240, 1926.

23 Loeb, J. Die Chemische Entwicklungserregung des tierischen Eies, Berlin, Julius Springer, 1909.

24 Warburg, O. Ueber Beeinflussung der Sauerstoffatmung, *Ztschr. f. physiol. Chem.* **70** 413, 1911.

division could be stopped in sea urchin eggs by the addition of 0.01 per cent phenylurethane, a procedure which did not appreciably affect the rate of oxygen consumption. Further, Meyerhof<sup>25</sup> could find no trace of heat liberated on the sudden killing of large numbers of bird erythrocytes. Nor could he demonstrate any extra heat production when growth was stopped and the oxygen consumption maintained at the same rate. Brown,<sup>26</sup> however, found that yeast while fermenting a given amount of sugar produced about 8 per cent less heat under aerobic than anaerobic conditions. Growth occurred under the former conditions and not under the latter. He therefore assumed that the difference in generated heat represented the energy of cell division and growth. He did not, however, prove the presence of stored energy in the yeast. Whitaker<sup>27</sup> recently demonstrated that fertilization and cell division are accompanied by an increase in oxygen consumption in the case of some eggs, while in others a marked decrease in the oxygen up-take is observed. It should be noted that fertilization may in some instances institute catabolic changes which are not present in the mitotic division of hematopoiesis. Except for the observations of Brown, the evidence indicates that nitrogenous substances may be extracted from the surrounding medium and incorporated into cell protoplasm without the use of more oxygen than is required for the life of the cells concerned. Also, the morphologic change of cell division with the formation of new living membranes can be accomplished without the use of a measurable amount of extra oxygen. Indeed, if these conditions did not obtain it would be very difficult to explain the findings of Breza, i.e., that the bone marrow uses less oxygen per unit of fat-free dry weight than most other organs. During adult life true cell division is obviously more rapid in hematopoietic tissue than in any other bodily structure.

Not only is it true that bone marrow "activity" is not responsible for a large oxygen consumption, but when rapid cell formation is separated from an equally rapid cell destruction, the former is actually accompanied by a decrease in the basal metabolic rate. In a previous communication we presented evidence of a decrease in total oxygen consumption during the rapid erythropoiesis of induced remissions in pernicious anemia. As yet unpublished results show a similar drop in the oxygen consumption of dogs during recovery from acute hemorrhagic anemia. This decrease in oxygen consumption occurs during a

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<sup>25</sup> Meyerhof, O. *Chemical Dynamics of Life Phenomena*, Philadelphia, J. B. Lippincott, 1924, p. 87.

<sup>26</sup> Brown, H. *Some Studies on Yeast*, *Ann. Bot.* **28**:197, 1914.

<sup>27</sup> Whitaker, D. M. *The Oxygen Consumption of Fertilized and Unfertilized Eggs*, *J. Gen. Physiol.* **15**: 167, 183 and 191, 1931.

positive nitrogen balance only if the urinary nitrogen is decreased and may be related to the fact that protein which is deposited exerts no specific dynamic effect<sup>28</sup> The oxygen consumption was determined during the postabsorptive period in all instances, however, so that the decrease in gaseous metabolism was more likely due to the general lowering of protein catabolism during the periods of blood regeneration It should be noted in this connection that the intact mammal probably differs in at least one important respect from unicellular organisms Amino-acids once absorbed into the mammalian body must be either deposited, metabolized or rarely excreted in the urine Therefore, failure to store protein makes a temporary increase in metabolism mandatory, barring excretion, and an environment of abnormally low temperature The cell membrane of unicellular organisms governs the intake of nitrogenous substance so that such substances probably cannot be forced on unicellular organisms in any way comparable to that seen in the intact mammalian body Regardless of interpretation, the fact remains that increased activity of the bone marrow where it can be separated from an equally rapid cell destruction has, in our hands, shown a decrease rather than an increase in the total oxygen consumption The objection might be raised that in leukemia the bone marrow is overactive in the production of leukocytes, while in pernicious and hemorrhagic anemias erythrocytes are being produced It should be remembered in this connection that the progenitors of both cell types are nucleated, and cell production in both instances is by mitotic division Furthermore, the decrease in oxygen consumption appears to be roughly proportional to the degree of nitrogen retention It is therefore apparent that the greater the number of active hematopoietic cells in the body the greater the rate of cell division and the greater the temporary nitrogen storage If cell destruction could be stopped, the foregoing process should lead to a definite saving of oxygen of sufficient magnitude to offset easily the oxygen requirements of the increased number of preformed cells

#### INFLUENCE OF THE ANEMIA OF LEUKEMIA ON THE TOTAL OXYGEN CONSUMPTION

It is perhaps noteworthy that Riddle and Sturgis<sup>7</sup> found no parallelism between the degree of anemia and the increase in metabolism in myelogenous leukemia, while Krantz and Riddle<sup>8</sup> noted such a relationship in the lymphatic type The anemia of leukemia is of the

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<sup>28</sup> Rubner, M, quoted by Lusk, G The Science of Nutrition, Philadelphia, W B Saunders Company, 1928, p 297 Hoobler, B R The Protein Need of Infants, Being Metabolism Studies of a Two Months' Old Infant Fed with Varying Proportions of Cow's Milk Protein, *Am J Dis Child* **10** 153 (Sept) 1915

myelophthisic type, and immature erythrocytes and even nucleated forms are quite common in the circulating blood. Erythrocytes containing a reticulum or showing diffuse basophilia have been shown to have a much greater oxygen consumption than normal adult erythrocytes. Warburg,<sup>29</sup> Harrop<sup>30</sup> and Wright<sup>31</sup> all agree on this point, and all agree that the percentage difference is very great. Warburg found that the erythrocytes of young rabbits, in which evidence of youth is more abundant than in human leukemia, may use thirty times as much oxygen as adult human erythrocytes. It must be remembered, however, that the gaseous metabolism of normal human erythrocytes is extremely low. In spite of such a profound percentage increase, the difference between the total oxygen consumption of the normal erythrocytes of the body and a similar number of immature erythrocytes from young rabbits would be sufficient to raise the basal metabolic rate only 0.8 per cent. The total oxygen consumption is within a wide range independent of the amount of circulating hemoglobin. Increased erythropoiesis would lower the oxygen consumption. Increased destruction of erythrocytes might increase the metabolism, but evidence for the presence of this process is certainly not a marked feature in leukemia.

#### THE INFLUENCE OF TOXIC FACTORS

Grafe<sup>2c</sup> observed a patient with aleukemic myelosis in whom the basal metabolic rate was 29 per cent above normal. He considered that the aforementioned factors were insufficient to account for this increase in oxygen consumption since one factor which he considered to be of great importance, i. e., increase in circulating leukocytes, was entirely absent. He therefore suggested the possibility of some "toxic" factor which increased metabolism. In later publications, however, he decided that it was not necessary to assume the presence of toxic factors.<sup>2d</sup> So far as we are aware, no specific toxic substance has been isolated in leukemia, much less a specific metabolism stimulating substance. If the intermediary products of increased or aberrant protein catabolism can be considered toxic, we would then agree to the presence of a toxic factor. In the absence of any tangible evidence favoring a specific toxic factor, it seems futile and unnecessary to theorize.

The following is a summary of the calculated effects of previously mentioned factors which have been suggested to explain the increased

29 Warburg, O. Zur Biologie der roten Blutzellen, *Ztschr f physiol Chem* 59 112, 1909

30 Harrop, G. A., Jr. The Oxygen Consumption of Human Erythrocytes, *Arch Int Med* 23 745 (June) 1919

31 Wright, G. P. Factors Influencing Respiration of Erythrocytes, Mammalian Reticulocytes, *J Gen Physiol* 14:201, 1930

gaseous metabolism in leukemia The calculations are based on the Aub-Du Bois standard for a man, aged 50, height, 150 cm, and weight, 70 Kg The blood volume is computed according to average figures, i e, 7 per cent of the body weight and the specific gravity of the blood is assumed to be 1 060 The patient is further assumed to have leukemia with a basal metabolic rate 50 per cent above normal and a 35 per cent increase in pulse rate

- 1 Increased cardiac rate—plus 1 to 2, per cent
- 2 Increased respiratory rate—plus 0 to 1 per cent
- 3 Increased circulating leukocytes—plus 3 per cent
- 4 Increased "infiltrated" leukocytes—plus 6 per cent
- 5 Increased extent of hematopoietic tissue—plus 6 to 9 per cent
- 6 Increased activity of hematopoietic tissue—minus 10 to 25 per cent
- 7 Increased respiration of young erythrocytes—plus 0 8 per cent

We cannot, of course, claim a high degree of accuracy for these calculations They include numerous assumptions, but we have tried to make our assumptions generous Even though we assume errors of great magnitude in transferring the results of in vitro experiments to conditions in vivo, it is still apparent that the algebraic sum of the effects of factors considered here is entirely inadequate to account for the enormous increases in oxygen consumption which are commonly found in leukemia

It therefore behooves us to look elsewhere for a factor or factors which might better explain the observed changes in oxygen consumption in leukemia as well as in other blood dyscrasias The necessity for a more adequate explanation of the altered gaseous metabolism in leukemia is also apparent on the basis of clinical observations Patients with widespread leukemia fairly frequently have a basal metabolic rate below the accepted normal average Also, patients with pernicious anemia may have basal rates in the lower ranges of normal at a time when the entire bone marrow is filled by closely packed cells, many of which are nucleated For the present we choose to ignore such intangible possibilities as a toxic factor and an altered metabolic function of the spleen We have turned our attention to the obvious increase in protein catabolism which exists in leukemia and have attempted to separate the effects of this process from those of concomitant and equally rapid anabolic processes

#### METHODS AND RESULTS

The data presented in this communication were obtained by eight studies on six patients with leukemic myelosis and by two periods of

study on a patient with lymphocytic lymphoma with leukemia (lymphatic leukemia) In six instances the observations included daily basal metabolic rates (Haldane-Tissot), nitrogen balances with nitrogen partitions and phosphorus balances Control periods immediately preceded and were continuous with the periods following irradiation On three occasions hourly determinations of the basal metabolic rate were made during a control day, and immediately after irradiation The remaining observation includes daily studies of the nitrogen balance and oxygen consumption before and after the surgical removal of about 500 Gms of lymphoid tissue The diets were low in purine but were not constant

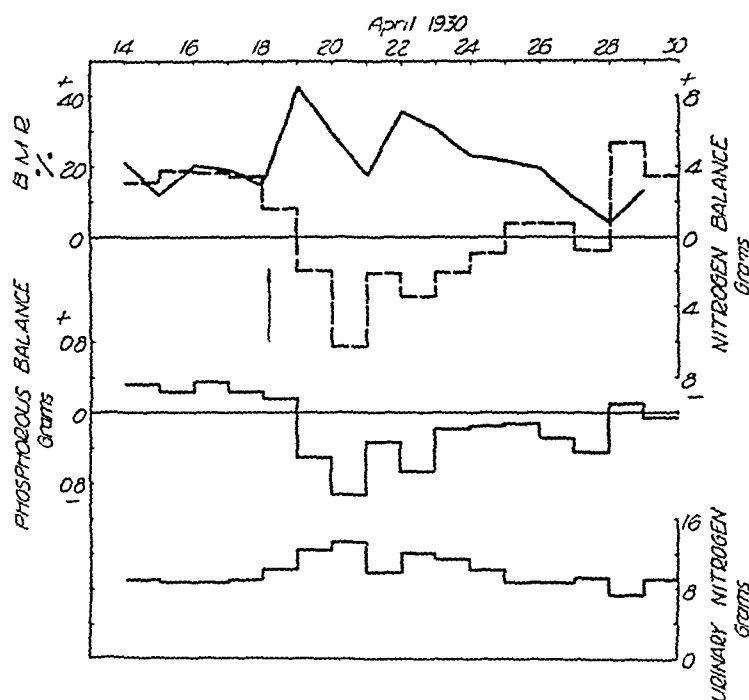


Chart 1—Curves obtained during metabolic study in case 1 The arrow indicates irradiation In charts 1 to 7, the solid line indicates the basal metabolic rate, the broken line, the nitrogen balance

owing to variations in appetite following roentgen treatment, The results are shown in the accompanying charts and tables

CASE 1—E M, a white man, aged 31, during the course of a rather trivial infection in the thigh in 1921 had a leukocyte count of 48,000 per cubic millimeter but differential studies were not made at that time Leukemic myelosis was diagnosed in 1927, at which time the leukocytes numbered 640,000 per cubic millimeter A total of thirty-one roentgen treatments were given during the three year period preceding our observations, which were begun on April 14, 1930, on April 18, a single dose (600 roentgens as measured in air) was given equally divided between the ventral and dorsal aspects of the splenic area The spleen decreased about 4 cm in its long diameter and about 6 cm in its transverse diameter during the succeeding twelve days



TABLE 1—Data in Case 1

Days	Tempera- ture, Month, F	Pulse Rate, per Min	Respira- tory Rate, per Min	Respira- tory Quo- tient	Basal Metabolic Rate, per Cent	Caloric Intake	Great Innec, Gm of Nitrogen	Uric Acid, Gm of Nitrogen	Urea, Gm of Nitrogen	Am- monia, Gm of Nitrogen	Total Urinary Nitrogen, Gm	Nitro- gen in Stools, Gm	Nitrogen Balance, Gm	Erythro- cytes, per O Mm	Leuko- cytes, per O Mm	Phosphorus Balance, Gm
1	98.0	64	12	0.703	+21.0	2,696	0.556	0.234	6.874	0.592	8.938	5.206	+3.272	3,800,000	57,600	+0.349
2	98.8	72	14	0.829	+13.0	2,774	0.679	0.309	5.170	0.542	8.830		+3.848	3,400,000	73,000	+0.246
3	98.4	72	12	0.780	+20.2	2,774	0.526	0.223	6.745	0.459	8.889		+3.788	3,950,000	81,500	+0.367
4	98.4	68	14	0.772	+19.1	2,774	0.518	0.190	6.369	0.485	9.139		+3.588	3,240,000	70,800	+0.244
5*	99.0	68	12	0.780	+14.9	2,698	0.599	0.276	7.613	0.546	10.462	5.054	+1.740	2,800,000	31,800	+0.171
6	98.2	72	16	0.799	+43.2	2,198	0.553	0.334	7.412	0.517	12.683		-1.991			-0.501
7	98.0	72	16	0.745	+29.6	2,052	0.536	0.357	9.937	0.825	13.345		-6.253			-0.838
8	98.0	72	14	0.778	+17.7	2,390	0.389	0.281	6.333	0.488	9.925		-2.038			-0.333
9	97.4	64	14	0.739	+35.9	2,338	0.634	0.290	10.154	0.934	12.228	6.604	-3.457	3,050,000	29,500	-0.678
10	97.8	64	16	0.838	+31.1	2,540	0.554	0.271	8.733	0.821	11.338		-2.056	3,400,000	22,000	-0.191
11	98.0	64	12	0.745	+23.2	2,617	0.478	0.246	7.070	0.714	10.283		-0.813			-0.142
12	98.0	64	12	0.826	+21.5	2,617	0.492	0.238	6.449	0.615	8.708		+0.761			-0.137
13	98.0	60	16	0.749	+19.2	2,586	0.486	0.272	6.618	0.643	8.727	6.604	+0.712	3,100,000	15,400	-0.291
14	97.2	60	12	0.786	+11.7	2,543	0.515	0.323	6.579	0.618	9.234		-0.836	3,230,000	12,100	-0.456
15	97.2	60	12	0.851	+4.0	2,774	0.438	0.219	6.983	0.576	7.405		+5.474	3,450,000	17,600	+0.122
16	97.0	64	16	0.782	+12.4	2,774	0.481	0.244	7.289	0.523	9.261		+3.617	3,490,000	15,900	-0.061

\* Roentgen therapy (600 roentgens) following determination of the basal metabolic rate. Irradiation was followed by a rather prolonged increase in the urinary nitrogen with only a moderate decrease in the caloric intake. The oxygen consumption reflected the endogenous nitrogen catabolism rather closely. The lack of correlation between changes in the oxygen consumption and changes in the temperature and the pulse and respiratory rates should be noted in all cases.

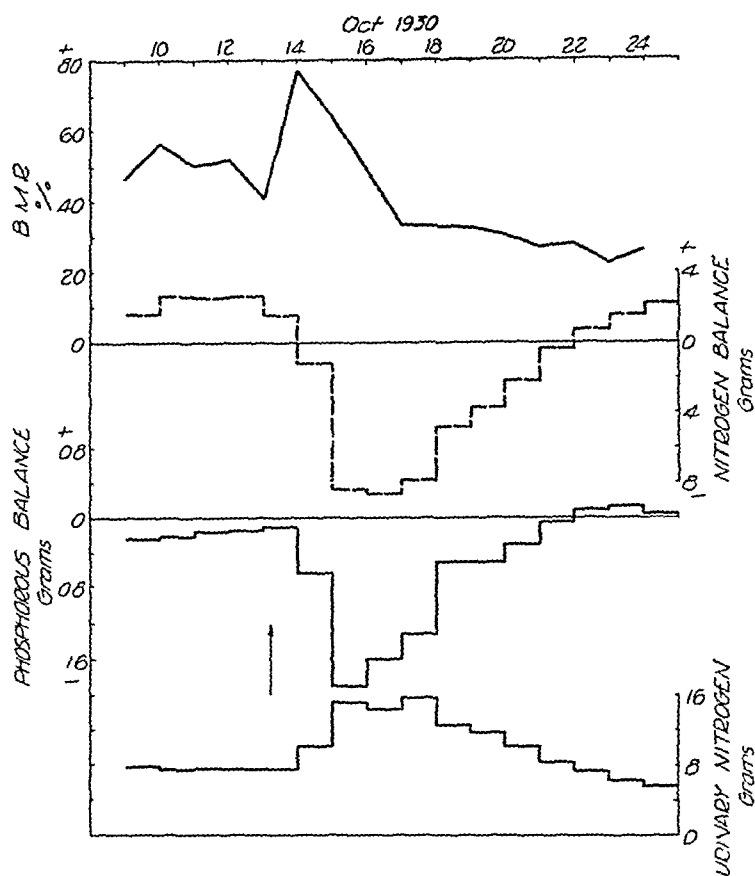


Chart 2—Curves obtained during metabolic study in case 2 The arrow indicates irradiation

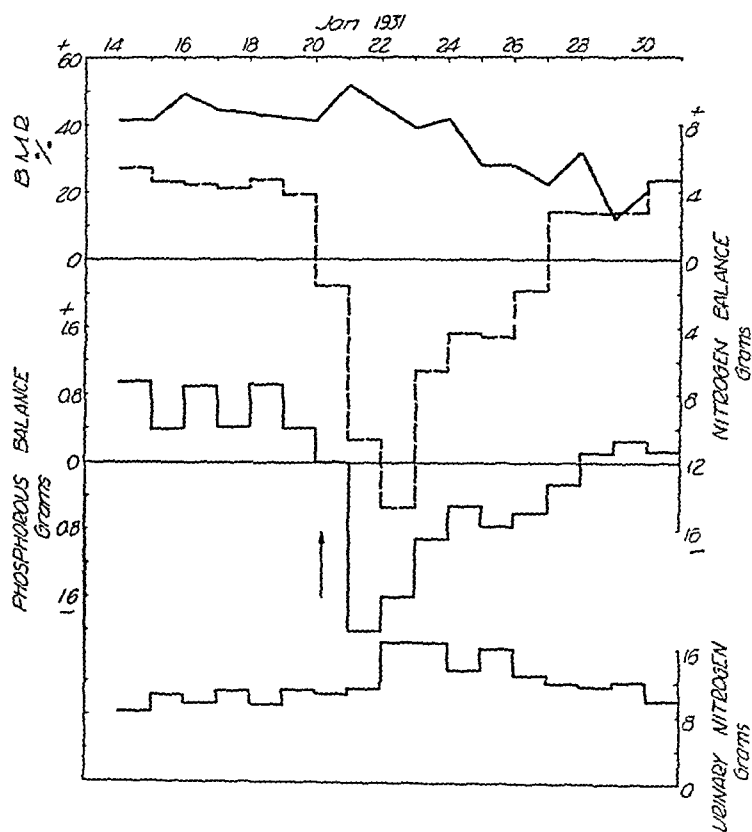


Chart 3—Curves obtained during metabolic study in case 3 The arrow indicates irradiation

TABLE 2—Data in Case 2

Days	Tempera- ture, Mouth, F	Pulse Rate, per Min	Respira- tory Rate, per Min	Respira- tory Quo- tient	Basal Metabolic Rate, per Cent	Caloric Intake	Great urine, Gm of Nitrogen	Uric Acid, Gm of Nitrogen	Urea, Gm of Nitrogen	Am- monia, Gm of Nitrogen	Total Urinary Nitrogen, Gm	Nitro- gen in Stools, Gm	Nitrogen Balance, Gm	Erythro- cytes, per C Mm	Leuko- cytes, per C Mm	Phosphorus Balance, Gm
1	99.4	74	16	0.730	+45.8	2,330	0.344	0.160	6.146	0.381	7.904	3.689	+1.786	2,940,000	407,000	-0.366
2	98.8	76	16	0.713	+56.2	2,649	0.333	0.171	5.610	0.349	7.448		+2.702	3,120,000	454,000	-0.209
3	98.4	74	18	0.748	+50.1	2,649	0.355	0.182	5.561	0.306	7.512		+2.638	2,980,000	411,000	-0.150
4	98.6	72	16	0.755	+52.0	2,649	0.374	0.181	5.106	0.319	7.437		+2.712	3,150,000	432,000	-0.152
5*	99.0	72	16	0.748	+41.3	2,340	0.357	0.204	5.708	0.423	7.663	4.270	+1.596	2,750,000	439,000	-0.091
6	98.6	76	16	0.792	+77.4	2,316	0.328	0.310	7.862	0.561	10.223		-1.117	2,930,000	363,000	-0.773
7	98.6	80	18	0.733	+64.4	2,005	0.324	0.272	11.188	0.622	15.162		-8.465	2,780,000	344,000	-1.922
8	98.6	76	16	0.822	+48.9	1,803	0.301	0.222	10.355	0.645	14.327		-8.560	2,730,000	373,500	-1.587
9	98.6	72	16	0.756	+32.9	2,320	0.321	0.180	11.849	0.768	15.628	3.633	-7.976	2,460,000	246,500	-1.272
10	98.6	72	16	0.774	+32.5	2,475	0.296	0.166	9.167	0.706	12.685		-4.765	2,360,000	236,000	-0.535
11	98.6	70	16	0.803	+31.8	2,315	0.293	0.175	9.363	0.685	11.543		-3.756	187,000	187,000	-0.498
12	98.2	68	14	0.767	+30.0	2,431	0.284	0.199	7.253	0.659	10.246		-2.349	183,000	183,000	-0.288
13	98.0	70	16	0.838	+26.5	2,478	0.273	0.123	6.236	0.619	8.330	3.633	-0.303	157,000	157,000	-0.032
14	98.0	68	14	0.829	+27.7	2,478	0.282	0.167	5.367	0.475	7.316		+0.710	128,000	128,000	+0.112
15	98.0	68	14	0.844	+21.7	2,478	0.264	0.178	4.230	0.589	6.480		+1.547	125,000	125,000	+0.139
16	99.0	68	16	0.776	+25.8	2,478	0.325	0.201	4.588	0.532	5.750		+2.276	130,500	130,500	+0.053

\* Roentgen therapy (500 roentgens) following determination of the basal metabolic rate. The changes following irradiation were the same as in case 1. If, as we contend, the period of increased oxygen consumption coincides with the height of induced protein catabolism, it would then appear that excretion of end products may be considerably delayed. The nonprotein nitrogen of the blood was not followed.

TABLE 3—Data in Case 3

D <sub>1</sub> 's	Tempera- ture, Month, F	Pulse Rate, per Min	Respira- tory Rate, per Min	Respira- tory Quo- tient	Basal Metabolic Rate, per Cent	Caloric Intake	Great Urine, Gm of Nitrogen	Uric Acid, Gm of Nitrogen	Urea, Gm of Nitrogen	Am- monia, Gm of Nitrogen	Total Urinary Nitrogen, Gm	Nitro- gen in Stools, Gm	Nitrogen Balance, Gm	Drythro- cytes, per O Mm	Leuko- cytes, per O Mm	Phosphorus Balance, Gm
1	99.0	68	12	0.767	+40.5	3,503	0.479	0.193	6.928	0.361	8.317	7.623	+5.181	2,510,000	320,800	+0.967
2	99.2	72	16	0.771	+40.9	3,308	0.659	0.115	7.897	0.546	10.282		+4.632			
3	99.2	68	16	0.739	+49.2	3,503	0.550	0.127	6.901	0.403	9.311		+4.458			
4	99.2	72	16	0.715	+44.0	3,308	0.669	0.207	7.486	0.562	10.691		+4.219			
5	99.4	70	16	0.735	+43.3	3,503	0.490	0.195	7.141	0.167	9.077		+4.721			
6	99.2	72	16	0.739	+42.3	3,308	0.651	0.167	8.158	0.513	11.019		+3.861			
7*	99.6	72	12	0.738	+40.5	2,465	0.591	0.241	8.226	0.591	10.505	5.003	-1.454	2,820,000	792,000	-0.001
8	99.8	76	16	0.709	+52.2	915	0.570	0.231	8.407	0.656	11.097		-10.708			
9	99.6	76	16	0.717	+44.6	1,154	0.605	0.215	10.383	0.731	16.704		-13.697			
10	99.0	72	14	0.730	+38.9	2,106	0.690	0.250	12.887	0.756	16.717		-6.457			
11	99.2	68	14	0.737	+11.5	2,065	0.497	0.246	9.832	0.735	13.416		-1.328			
12	99.2	68	12	0.766	+27.7	2,773	0.571	0.273	11.659	0.911	15.990		-1.470			
13	99.0	61	12	0.771	+28.3	2,700	0.550	0.192	9.112	0.761	12.810	7.650	-1.805	2,890,000	125,000	-0.603
14	98.6	61	12	0.770	+21.8	3,221	0.599	0.199	9.215	0.830	11.904		+2.752			
15	99.2	64	12	0.732	+31.5	3,366	0.656	0.209	8.353	0.871	11.062		+2.712			
16	98.6	68	14	0.713	+11.9	3,540	0.562	0.187	8.421	0.693	12.076		+2.833			
17	98.6	64	16	0.833	+19.6	3,352	0.705	0.160	7.303	0.851	9.917		+4.712			
18	98.0	64	12	0.850	+11.6	3,532										

\* Roentgen therapy (500 roentgens) following determination of the basal metabolic rate. Irradiation was followed by a marked decrease in food intake so that a moderate increase in urinary nitrogen led to a marked loss of nitrogen from the body. The excretion of the excess nitrogen was more prompt than in cases 1 and 2. The induced protein catabolism may have been largely accomplished within the twenty-two hour period which elapsed between irradiation and the subsequent determination of the oxygen consumption.

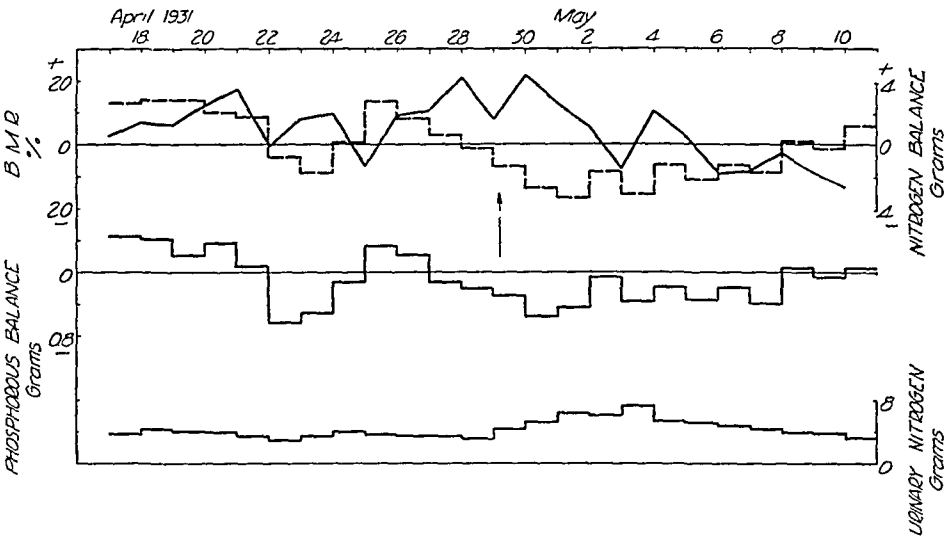


Chart 4—Curves obtained during metabolic study in case 4 The arrow indicated irradiation

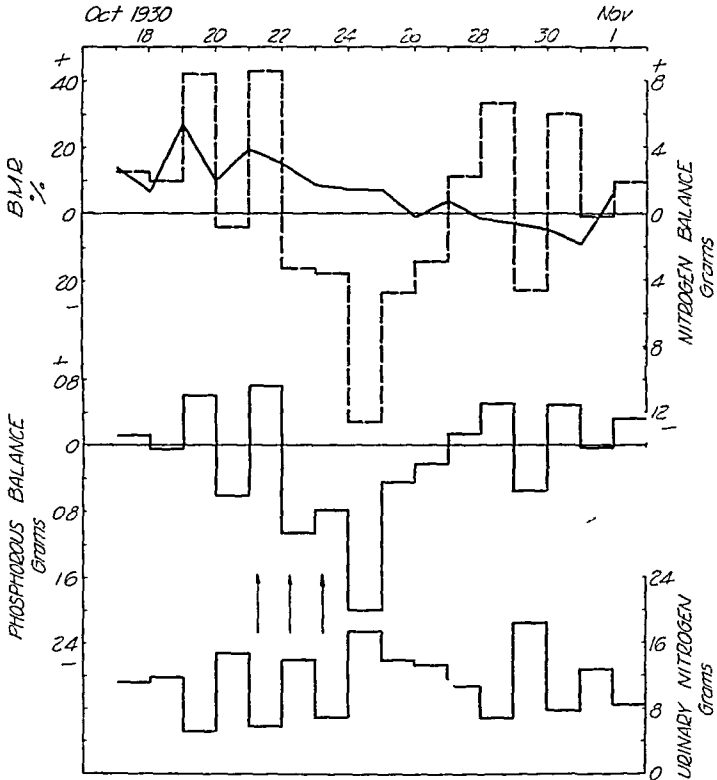


Chart 5—Curves obtained during metabolic study in case 5 The arrows indicate irradiation

TABLE 4—Data in Case 4

Days	Temperature Mouth, F	Pulse Rate, per Min	Respiratory Rate, per Min	Respiratory Quo- tient	Basal Metabolic Rate, per Cent	Calorie Intake	Great Intake, Gm of Nitrogen	Uric Acid, Gm of Nitrogen	Urea, Gm of Nitrogen	Am- monia, Gm of Nitrogen	Total Urinary Nitrogen, Gm	Nitro- gen in Stool, Gm	Nitrogen Balance, Gm	Lympho- cytes, per O Mm	Leuko- cytes, per O Mm	Phosphorus Balance, Gm
1	98.6	88	16	0.762	1.25	1,756	0.236	0.211	2.093	0.261	3.726	1.181	1.2615	3,620,000	375,000	+0.160
2	99.2	84	16	0.710	+7.2	1,730	0.266	0.203	2.802	0.251	4.267		1.2000	3,120,000	316,000	+0.193
3	99.0	88	11	0.711	+6.5	1,711	0.225	0.188	2.935	0.222	4.111		+2.916	3,760,000	333,000	+0.211
4	99.0	84	16	0.696	1.12	1,788	0.242	0.137	2.819	0.319	3.963		+2.017	3,800,000	314,000	+0.370
5	99.1	84	16	0.705	+17.7	1,418	0.215	0.125	2.411	0.385	3.170	1.181	+1.766	3,410,000	309,500	+0.086
6	99.2	80	16	0.712	-0.5	470	0.211	0.111	1.925	0.384	3.003		-8.312	3,800,000	322,500	-0.627
7	99.1	84	16	0.704	1.87	701	0.203	0.103	2.379	0.297	3.528		-1.899	3,530,000	366,000	-0.506
8	99.2	84	16	0.719	+10.1	976	0.213	0.119	3.085	0.292	4.069		+0.111	3,380,000	380,000	-0.122
9	98.6	80	16	0.704	-6.5	1,461	0.238	0.219	2.611	0.285	3.718	1.661	+2.805	4,500,000	380,000	+0.341
10	99.1	84	16	0.728	+9.5	1,153	0.240	0.119	2.487	0.383	3.621		1.571	3,210,000	316,000	+0.238
11	99.6	84	16	0.711	+11.0	987	0.246	0.188	2.681	0.403	3.559		+0.637	3,590,000	338,000	-0.117
12	99.2	84	16	0.700	+21.7	852	0.230	0.218	2.377	0.312	3.203		-0.189	3,800,000	326,000	-0.180
13*	99.6	84	16	0.755	+8.0	583	0.241	0.153	2.984	0.322	4.357	1.693	-1.262	3,690,000	371,000	-0.273
14	99.2	84	18	0.711	+22.1	638	0.279	0.204	3.888	0.501	5.252		-2.696	3,750,000	373,000	-0.564
15	99.6	84	16	0.700	+13.1	734	0.274	0.224	4.721	0.112	6.936		-3.316	3,270,000	218,000	-0.431
16	99.1	88	16	0.725	+6.0	912	0.281	0.216	4.951	0.511	6.112		-1.612	3,900,000	288,400	-0.062
17	99.1	84	16	0.706	+7.5	868	0.264	0.187	5.678	0.605	7.253	1.990	-3.140	3,890,000	276,000	-0.371
18	99.0	80	16	0.699	+10.1	913	0.256	0.146	4.170	0.533	5.586		-1.242	3,200,000	170,000	-0.183
19	98.8	80	16	0.716	+3.0	772	0.223	0.101	3.952	0.439	5.105		-2.235	3,610,000	186,500	-0.339
20	98.8	76	14	0.728	-8.8	870	0.221	0.146	3.493	0.508	4.794		-1.137	4,240,000	181,500	-0.170
21	98.8	72	14	0.706	-6.1	679	0.227	0.144	2.989	0.511	4.270	1.990	-1.611	3,410,000	182,500	-0.380
22	98.8	72	16	0.716	-2.2	1,025	0.218	0.134	2.951	0.733	3.998		+2.510	3,670,000	139,500	+0.077
23	98.6	72	16	0.706	-8.1	900	0.226	0.133	3.031	0.345	3.932		-0.213	3,760,000	127,000	-0.056
24	99.6	80	16	0.701	-12.8	955	0.187	0.117	2.611	0.286	3.307		+1.244	3,720,000	122,000	+0.062

\* Roentgen therapy (500 roentgens) following determination of the basal metabolic rate. The increase in oxygen consumption following irradiation was not great, a circumstance which is in keeping with the small increase in urinary nitrogen and the low caloric intake. The reaction of this patient may have been influenced by a roentgen treatment which was given eleven days before the metabolic observations were begun.

TABLE 5—Data in Case 5

Days	Tempera- ture, F	Pulse Rate, per Min	Respira- tory Rate, per Min	Basal Metabolic Rate, per Cent	Calorie Intake	Creat- inine, Gm of Nitrogen	Uric Acid, Gm of Nitrogen	Urea, Gm of Nitrogen	Am- monia, Gm of Nitrogen	Total Urinary Nitrogen, Gm	Nitro- gen in Stools, Gm	Nitrogen Balance, Gm	Erythro- cytes, per C Mm	Leuko- cytes, per O Mm	Phosphorus Balance, Gm
1	98.6	68	10	+14.5	2,763	0.485	0.117	8.885	0.691	11.278	5.208	+2.037	3,910,000	82,500	+0.137
2	98.6	68	12	+6.9	2,878	0.597	0.173	8.751	0.662	11.923		+2.016		65,000	-0.035
3	98.4	68	12	+27.0	2,878	0.310	0.101	3.800	0.337	5.401		+8.538		67,500	+0.605
4	98.4	68	12	+9.6	2,878	0.790	0.211	10.555	0.631	14.756		-0.816		56,500	-0.602
5*	98.2	72	12	+19.4	2,878	0.829	0.086	4.971	0.294	6.207	1.136	+8.512		31,500	+0.710
6*	97.8	72	12	+14.7	2,157	0.790	0.163	10.497	0.651	13.941		-3.295			-1.077
7*	97.8	68	12	+7.9	1,185	0.321	0.096	5.982	0.436	7.484		-3.648		24,800	-0.783
8	98.2	64	12	+7.3	960	0.715	0.350	12.659	0.940	17.482		-12.648			-2.002
9	98.0	60	12	+6.5	1,866	0.852	0.191	10.807	0.717	13.916		-4.778			-0.455
10	98.0	60	12	-1.6	2,238	0.371	0.230	9.981	0.958	13.569		-2.989			-0.232
11	98.0	60	10	+3.5	2,386	0.472	0.134	8.082	0.930	10.563	6.902	+2.253		+0.151	
12	98.0	60	10	-1.2	2,688	0.321	0.065	4.929	0.590	6.785		+6.735		+0.502	
13	98.0	60	10	-3.0	2,725	0.910	0.260	14.196	1.764	18.396		-4.658		-0.567	
14	97.2	60	10	-5.0	2,776	0.508	0.090	6.055	0.704	7.806		+5.939		+0.485	
15	98.0	60	10	-9.6	2,601	0.677	0.164	9.722	1.098	12.875		-0.222		-0.029	
16	98.0	60	10	+6.2	2,160	0.594	0.126	6.601	0.612	8.169		+1.976		+0.326	

\* Roentgen therapy (total 1,000 roentgens in three days) The complete absence of increase in oxygen consumption in this patient led us to undertake experiments of the type seen in chart 8

CASE 2—N J, a white man, aged 55, had a condition diagnosed leukemic myelosis eighteen months before metabolic studies were begun, and during this interval fifteen or twenty roentgen treatments were given. The metabolic studies extended from Oct 2 to 24, 1930. On October 13, the patient received a single roentgen treatment (500 roentgens) equally divided between the ventral and dorsal

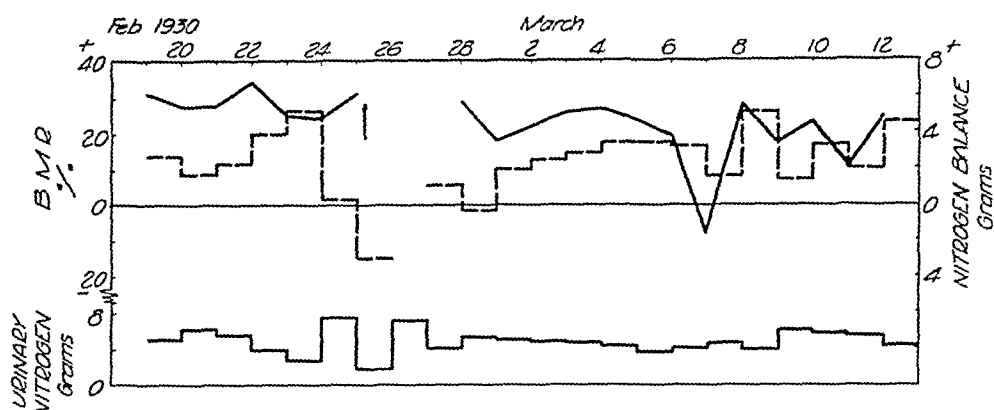


Chart 6—Curves obtained during the first metabolic study in case 6. The arrow indicates an operation followed by hemorrhage and transfusion.

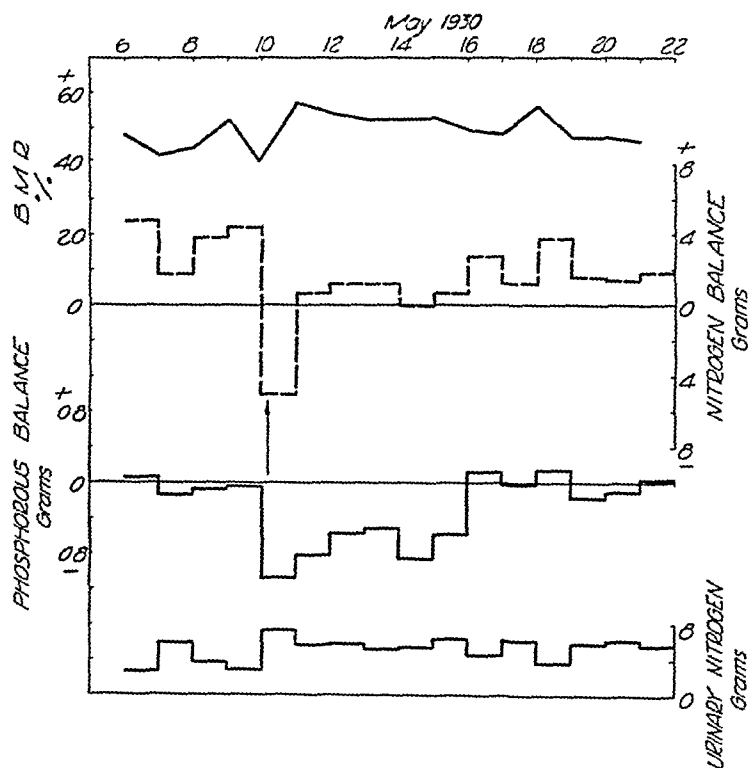


Chart 7—Curves obtained during the second metabolic study in case 6. The arrow indicated irradiation.

aspects of the splenic region. Seven days later the long diameter of the spleen had decreased about 9 cm.

CASE 3—E F, a white man, aged 40, had an enlarged spleen in June, 1930, but received no irradiation prior to the period of metabolic study, which extended from Jan 14 to 20, 1931. A single roentgen treatment (500 roentgens) was administered on January 20, and was equally divided between the ventral and



TABLE 6—Data in Case 6 Obtained During First Metabolic Study

Days	Temperature, F	Pulse Rate, Min	Respira- tory Rate, per Min	Respira- tory Quo- tient	Basal Metabolic Rate, per Cent	Caloric Intake	Great Innate, Gm of Nitrogen	Uric Acid, Gm of Nitrogen	Urea, Gm of Nitrogen	Am- monia, Gm of Nitrogen	Total Urinary Gm	Nitro- gen in Stools, Gm	Nitrogen Balance, Gm	Erythro- cytes, per C Mm	Leuko- cytes, per C Mm
1	97.6	68	16	0.717	+30.7	2,562	0.345	0.175	3.473	0.169	5.267	3.731	+2.872	3,320,000	110,000
2	97.6	72	16	0.707	+28.4	2,562	0.447	0.212	4.328	0.235	6.374		+1.765		
3	98.0	76	16	0.725	+28.0	2,562	0.395	0.119	4.271	0.293	5.656		+2.484		
4	97.0	72	16	0.694	+34.6	2,562	0.267	0.066	2.846	0.193	3.968		+4.172		
5	98.6	72	16	0.738	+25.3	2,562	0.100	0.048	1.873	0.141	2.764		+5.376		
6	98.4	72	16	0.719	+24.9	2,562	0.522	0.226	5.675	0.352	7.749		+0.391		
7*	98.2	80	16	0.723	+31.4		0.150	0.033	1.377	0.094	1.928	9.422	-2.871	3,100,000	100,500
8						1,214	0.451	0.117	5.245	0.411	7.194		-3.317		
9						1,282	0.260	0.046	2.716	0.221	4.147		+1.200		
10	98.0	88	16	0.705	+28.7	1,930	0.323	0.052	3.027	0.349	5.298		-0.233		
11	97.4	84	16	0.705	+17.1	2,595	0.375	0.048	3.206	0.382	5.281		+2.070		
12	98.0	78	16	0.719	+22.1	2,563	0.312	0.057	3.289	0.369	19.70		+2.589		
13	98.1	80	16	0.715	+26.3	2,676	0.293	0.050	3.322	0.343	1.882	8.231	+2.957	3,100,000	100,500
14	97.6	78	16	0.702	+27.1	3,033	0.320	0.079	3.287	0.280	4.351		+3.571		
15	97.0	76	16	0.740	+27.6	2,786	0.255	0.071	2.797	0.221	3.790		+3.511		
16	97.4	72	16	0.710	+18.8	2,402	0.299	0.039	2.967	0.249	4.155		+3.408		
17	97.2	72	16	0.797	-9.1	2,540	0.265	0.083	3.022	0.196	4.593		+1.766		
18	97.4	76	16	0.702	+27.1	3,120	0.253	0.068	2.969	0.251	3.906	8.231	+5.238	3,100,000	100,500
19	97.4	76	16	0.721	+16.1	2,673	0.421	0.101	4.147	0.295	6.086		+1.411		
20	98.0	72	18	0.724	+10.0	2,741	0.388	0.130	4.276	0.354	5.812		+3.352		
21	98.0	72	16	0.781	+23.2	2,891	0.331	0.080	3.975	0.404	5.449		+2.048		
22	97.8	74	16	0.715	+22.1	3,089	0.395	0.121	3.602	0.220	4.450		+4.714		

\* Operation, hemorrhage and transfusion. An attempt was made to compare the effects of surgical removal as contrasted with removal of tissue by irradiation. The hemorrhage and the transfusion interrupted the experiment at a crucial time.

TABLE 7—Data in Case 6 Obtained During Second Metabolic Study

Days	Tempera- ture, F	Pulse Rate, per Min	Respira- tory Rate, per Min	Respira- tory Quo- tient	Basal Metabolic Rate, per Cent	Caloric Intake	Great Inne, Gm of Nitrogen	Uric Acid, Gm of Nitrogen	Urea, Gm of Nitrogen	Am- monia, Gm of Nitrogen	Total Urinary Nitrogen, Gm	Nitro- gen in Stools, Gm	Nitrogen Balance, Gm	Erythro- cytes, per C Min	Leuko- cytes, per O Min	Phosphorus Balance, Gm
1	97.0	80	16	0.724	+48.1	2,137	0.106	0.088	2.155	0.100	2.833	3.220	+1.898	101,000		+0.061
2	97.8	80	18	0.730	+42.3	2,137	0.114	0.103	1.214	0.137	5.956		+1.777			-0.138
3	97.6	80	16	0.718	+41.6	2,137	0.219	0.118	2.732	0.219	3.760		+2.971			-0.075
4	97.4	80	18	0.732	+52.6	1,993	0.166	0.062	2.073	0.138	2.689		+1.407			-0.038
5*	97.0	80	16	0.715	+40.9	1,129	0.115	0.176	5.008	0.113	7.453	8.177	-5.097	118,000	2,550,000	-1.076
6	97.8	80	16	0.727	+57.4	2,063	0.208	0.135	4.090	0.372	5.819		+0.776			-0.827
7	98.0	80	16	0.725	+53.8	2,137	0.275	0.138	1.022	0.367	5.891		+1.233			-0.576
8	97.0	80	16	0.737	+52.2	2,063	0.253	0.143	3.616	0.288	3.390		+1.205			-0.529
9	97.6	80	16	0.776	+52.2	1,919	0.261	0.173	3.949	0.335	5.545	6.139	-0.006	102,000		-0.868
10	97.0	80	16	0.720	+52.8	2,137	0.301	0.113	4.628	0.319	6.357		+0.765			-0.577
11	97.8	80	16	0.728	+40.4	2,137	0.213	0.100	3.171	0.219	4.618		+2.864			+0.123
12	97.4	80	16	0.757	+48.1	2,137	0.280	0.134	4.881	0.354	6.292		+1.291			-0.034
13	98.0	76	16	0.697	+46.3	2,137	0.184	0.087	2.714	0.212	3.677	6.139	+3.836			+0.140
14	98.0	80	16	0.743	+47.2	2,137	0.285	0.121	1.200	0.373	5.840		+1.673			-0.156
15	98.4	80	16	0.731	+47.4	2,137	0.297	0.110	1.204	0.306	6.072		+1.441			-0.101
16	98.2	80	16	0.754	+45.6	2,137	0.293	0.111	1.206	0.316	5.661		+1.848			+0.045

\* Roentgen therapy (300 roentgens) following determination of the basal metabolic rate. The dose of roentgen rays was smaller and the responses in both nitrogen and oxygen consumption were smaller than in cases 1 and 2.

dorsal aspects of the splenic area. The long diameter of the spleen decreased 10 cm in the following seven days. The case was a characteristic example of leukemic myelosis.

CASE 4—I B, white woman, aged 49, had a condition diagnosed leukemic myelosis in July, 1930, and on April 6, 1931, received one roentgen treatment (200 roentgens). The period of metabolic study extended from April 17, to May 10, 1931. A single roentgen treatment (500 roentgens) was given on April 29, and was followed by a decrease of about 3 cm in the long diameter of the spleen.

CASE 5—In H B, a white man, aged 37, symptoms were first noted in January, 1930. The diagnosis of leukemic myelosis was established, and three roentgen treatments were given in March, and three more in July, 1930. Metabolic studies were begun on October 17, and roentgen treatments were given on October 21, 22 and 23. The three irradiations during the period amounted to 1,000 roentgens, and were limited to the splenic area. Seven days after the last treatment, the spleen had decreased about 6 cm in its long diameter.

CASE 6—G P, white man, aged 69, had enlarged lymph nodes that were discovered by the patient two and one-half years before our studies were begun. All of the characteristic features of lymphatic leukemia were present. Metabolic studies extended from February 19, to March 12, 1930. On February 25 a mass of lymphoid tissue 12 by 10 by 4 cm and weighing about 500 Gm was removed from the upper part of the sternum. Considerable blood was lost, necessitating a transfusion. A second metabolic study extended from May 6 to May 21, 1930. A dose of roentgen rays (300 roentgens) was given over the dorsal and ventral splenic areas on May 10. The long diameter of the spleen decreased only about 3 cm after this treatment.

#### COMMENT

A study of the charts will reveal that there are two phases in the response of leukemic patients to roentgen rays. Immediately after irradiation there is a decided negativity in the nitrogen and phosphorus balances. This state of affairs is contributed to by decreased food intake and increased protein catabolism. Occasionally the former factor is by far the larger, and this is especially true in case 5. Another variable factor in this connection is the speed with which protein is catabolized after irradiation. This may depend in part on the amount of irradiation applied and the susceptibility of the cells and in part on the efficiency of the catabolizing and excretory mechanisms of the patient. At least in case 5 in which the symptoms were of recent origin, the excess uric acid excretion was accomplished more rapidly than in cases of longer standing, such as cases 1 and 2. This observation suggested the possibility that the increased oxygen consumption of protein catabolism after roentgen therapy might follow a curve more or less like that seen after the ingestion of protein. In consequence, the oxygen consumption was determined at hourly intervals after smaller doses of roentgen rays, and the resultant curves are shown in chart 8. Taking into account the numerous variable factors, we interpret these data as showing that irradiation in leukemia leads to an increased oxygen consumption during the time that protein is actually being catabolized.

This is exactly what might be expected since Rubner<sup>32</sup> has shown that endogenous protein has the same specific dynamic effect as exogenous protein, and Kikkoi<sup>33</sup> was able to show an increase in basal metabolic rate after the ingestion of radium water. The duration and extent of the increased oxygen consumption after irradiation no doubt depends on the degree of protein catabolism induced and the speed with which the catabolic products are completely metabolized. Musser and Edsall<sup>34</sup> described the effect of irradiation on the metabolism of nitrogen and phosphorus in leukemia. Riddle and Sturgis<sup>7</sup> and Krantz and Riddle<sup>8</sup>

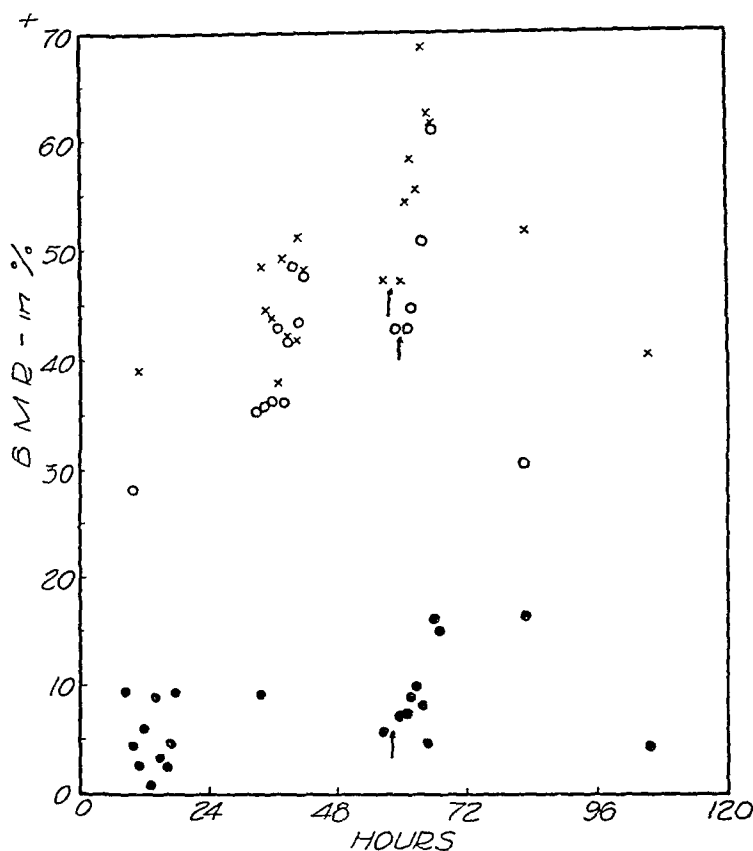


Chart 8—Curves obtained during metabolic studies. The arrows indicate the points at which roentgen ray treatments were given. The doses varied from 150 to 300 roentgens and were given over the splenic areas. During both control and treatment days food was withheld, and the basal metabolic rate was determined every hour. It will be noted that the patients with higher initial metabolic rates responded more promptly and to a greater degree than the one in whom the oxygen consumption was within normal limits before irradiation. The cross indicates the curve of N. J. (April 15, 1931), the open circle, the curve for H. B. (May 17, 1931), and the solid circle, the curve for I. B. (Dec. 8, 1931).

32 Rubner, M., quoted by Lusk, G. *The Science of Nutrition*, Philadelphia, W. B. Saunders Company, 1928, p. 282.

33 Kikkoi, T. *Ueber den Einfluss von Radiumemanation auf den Gesamtstoffwechsel im Organismus*, Radium, *Biol. Heilkunst* **1** 46, 1911.

34 Musser, J. H., and Edsall, D. L. *A Study of Metabolism in Leukemia Under the Influence of the X-Ray*, Univ. Pennsylvania M. Bull. **18** 174, 1905-1906.

found an occasional increase in basal metabolism in leukemic patients after irradiation, but we know of no previous systematic correlation of the two factors

The second phase of the postirradiation reaction in leukemia is the direct opposite of the first. There is a tendency toward retention of nitrogen and phosphorus and a lowering of the oxygen consumption. This is in accordance with the findings which obtain during remissions in pernicious anemia. Protein catabolism usually reached a lower level during this period than in the control period.

Without data of a more quantitative nature, it seems futile to try to establish whether or not the increase in oxygen consumption can be completely accounted for on the basis of protein catabolism. For such calculations it would be necessary to keep the patient in a respiratory calorimeter almost constantly until the catabolism of the protein is completed. Neither the oxygen consumption nor the endogenous nitrogen excretion remain constant for long at a time, and major fluctuations throughout the day may be missed by our method of study.

It is our purpose in these communications to point out that the formation of blood elements is associated with a lowered total oxygen consumption, while the destruction of these same elements causes an increased basal metabolic rate. However, the application of these two principles in an explanation of the increased metabolism of untreated leukemia is beset with difficulties. Brogsitter and Schmidt-Ott<sup>35</sup> showed that patients with lymphatic leukemia who were on a minimum nitrogen intake excreted 2.6 to 3.2 mg. of uric acid per kilogram per day instead of the normal from 1.6 to 2.8 mg. per kilogram per day. The uric acid excretion of a patient with leukemic myelosis was found to be 4.8 mg. per kilogram per day under similar circumstances. These investigators estimated that leukocytes were being formed and destroyed at from thirty-six to fifty-six times the normal rate and were consequently forced to conclude that part of the nitrogen-containing material in the leukocytes was used over and over again. However, it would appear a priori that such nitrogen-containing elements which were to be reutilized would probably not be broken down past the amino-acid stage. We have no accurate information as to the amount of energy involved in the dissociation and detoxification of leukocyte proteins when this is done elsewhere than in the gastro-enteric tract. The normal destruction of leukocytes is accomplished largely at least by excretion into the gastro-enteric tract where they are digested and reabsorbed. The number of leukocytes in the saliva is increased after roentgen treatment

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35 Brogsitter, A. M., and Schmidt-Ott, A. Ueber den Eiweissstoffwechsel bei Leukämien im Stickstoffminimumversuch, *Deutsches Arch. f. klin. Med.* **170** 1, 1931.

in leukemia, but it seems unlikely that all cells disappearing from the spleen after irradiation could find their way into the gastro-enteric tract. On teleologic grounds one might expect a disturbance in metabolism from the breaking up of leukocytes within the physiologic limits of the body instead of in the digestive tract. Experimental evidence on this point is difficult to obtain because the parenteral introduction of protein is so frequently complicated by "foreign protein reactions."

The experimental work of Mann<sup>36</sup> and his co-workers, of Dock,<sup>37</sup> of Meyerhof, Lohmann and Meier<sup>38</sup> and of Bornstein and Roesse<sup>39</sup> all tends to show that deamidization of amino-acids by the liver is necessary before the specific dynamic effect of these substances becomes apparent. If these findings are correct, it probably would not be possible for the amino-acids which result from leukocyte destruction to exert a specific dynamic effect and to be reutilized subsequently. There seems to be no good reason for assuming that the resynthesis of amino-acids is of any greater magnitude in leukemia than in the normal. Boothby, Sandiford and Giffin<sup>40</sup> found an increased amino-acid content of the blood in leukemia. Rapport and Katz<sup>41</sup> found that the addition of an amino-acid to the defibrinated blood with which an isolated hindleg was perfused, increased the oxygen up-take of the tissue. These two observations would suggest that the increased oxygen consumption of leukemia might be due to a catalytic effect of circulating amino-acids. However, Bornstein<sup>39</sup> was unable to confirm the work of Rapport and Katz, which is also directly opposed to the findings of other investigators<sup>42</sup>.

That the metabolism of amino-acids derived from ingestion of protein is associated with an increased oxygen consumption is certainly not debatable. A similar rise is seen if the pure amino-acids are injected intravenously. Under ordinary circumstances, the specific dynamic action of food is intentionally missed by determining the basal metabolic

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36 Mann, F. C., Wilhelmj, C. M., and Bollman, J. L. Studies on the Physiology of the Liver, *Am J Physiol* **81** 496, 1927, **87** 497, 1928.

37 Dock, W. The Relative Increase in Metabolism of the Liver and Other Tissues During Protein Metabolism in the Rat, *Am J Physiol* **97** 117, 1931.

38 Meyerhof, O., Lohmann, K., and Meier, R. Ueber die Synthese des Kohlenhydrats im Muskel, *Biochem Ztschr* **157** 459, 1925.

39 Bornstein, A., and Roesse, H. F. Ueber die Beeinflussung des Sauerstoffverbrauches überlebender Organe durch Glykokoll, *Arch f ges Physiol* **223** 498, 1929.

40 Boothby, W. M., Sandiford, I., and Giffin, H. Z. The Amino-Acid Nitrogen in the Blood and Its Possible Relation to the Elevated Metabolism in Myelogenous Leukemia, *J Biol Chem* **55** xxiii, 1923.

41 Rapport, D., and Katz, L. N. The Effect of Glycine upon the Metabolism of Isolated Perfused Muscle, *Am J Physiol* **80** 185, 1927.

42 Maun and others<sup>36</sup> Dock<sup>37</sup>

rate during the postabsorptive period. In leukemia metabolism of amino-acids from broken down leukocytes is perhaps a variable but more or less constant factor which cannot be avoided in the determination of the basal metabolic rate. The protein turn over in leukocyte destruction is perhaps large enough to simulate the conditions which obtain in the "secondary rise" of Rubner or the "luxus consumption" of other writers. It is possible that immature cells have a greater rate of destruction than the more adult forms, and this may be an explanation for the relationship observed by previous investigators<sup>43</sup> between the number of circulating immature cells and the basal metabolic rate. There is much evidence that an undue increase in endogenous protein catabolism may cause a rate of oxygen consumption of a magnitude comparable to that seen in leukemia. This is perhaps best shown in phlorhizin diabetes<sup>44</sup>.

The increased oxygen consumption which follows irradiation of the spleen in leukemia is no doubt the result of increased protein catabolism. Such factors as cell growth, cell activity and increased numbers of leukocytes are, we believe, utterly inadequate as an explanation for the increased gaseous metabolism in leukemia. We believe, therefore, that the virtue of logic is with the contention that protein catabolism is in some way responsible for the major part of the increased oxygen utilization of the leukemic patient. The mechanism by which protein catabolism brings this change about is not clear. The effect of autolysis of leukocytes in tissue is one of the unknown and possibly important factors. Until the intermediary metabolism of protein in general is better understood, the details will remain obscure.

#### SUMMARY

An hematopoietic disease (leukemia) has been studied before and immediately after irradiation. Immediately after roentgen treatment there is increased protein catabolism which is derived largely from the destruction of nucleated cells. The evidence for this statement is to be found in the increased excretion of uric acid and perhaps of phosphorus. This accentuation of cellular destruction is associated with an increase in the total oxygen consumption of the patient in most, if not all, instances. In the instance (case 5) in which no increase was observed, it appears that the catabolic processes were prompt and may have been completed within twenty-four hours after the treatment. The secondary phase which follows is characterized by increased nitrogen retention and a lowered total oxygen consumption.

43 Riddle and Sturgis<sup>7</sup> Krantz and Riddle<sup>8</sup> Gunderson<sup>9</sup>

44 Lusk, G. Animal Calorimetry. An Investigation into the Causes of the Specific Dynamic Action of Foodstuffs, *J Biol Chem* **20** 555, 1915

Evidence is presented to show that such factors as increased numbers of leukocytes in the body, increased activity of the hematopoietic tissues and anemia are entirely inadequate as explanations of the increased oxygen consumption in leukemia. We wish to suggest that protein catabolism is in some way the major factor in the increased gaseous metabolism of leukemia. The details as to how this cause brings about the result which it does are not clear. The evidence presented here substantiates the following previously suggested hypothesis. There is a direct causal relationship between the increase in nitrogen catabolism and the increased oxygen consumption and a similar relationship of cause and effect between nitrogen storage and decrease in oxygen requirement.



# TREATMENT OF POLYCYTHEMIA VERA (ERYTHREMIA) WITH SOLUTION OF POTASSIUM ARSENITE

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Arsenic has been used extensively for hundreds of years in the treatment of many diseases. During the past one hundred and fifty years it has been employed most commonly in the form of solution of potassium arsenite, U S P (Fowler's solution). One of its chief uses, prior to a few years ago, was to combat anemia. There appears to be no doubt that prior to the discovery by Minot and Murphy<sup>1</sup> of the effectiveness of liver in pernicious anemia, solution of potassium arsenite properly given was responsible for many remissions produced in this disease.<sup>2</sup> Hence, arsenic gained the reputation of being an anti-anemic drug and was employed, frequently with a measure of success, in the treatment of certain types of anemia. On the basis of these facts, it would seem to be paradoxical that any favorable effect could be elicited by its administration to patients suffering from polycythemia vera.

No actual demonstration of the value of potassium arsenite or other preparations of arsenic in polycythemia vera can be found in the literature, although Turk,<sup>3</sup> in 1904, suggested the use of arsenic, having found, in one case of polycythemia vera, that the administration of solution of potassium arsenite in doses of 30 minims (1.9 cc) daily was associated with a decrease in the hemoglobin concentration from 22 to 18 Gm per hundred cubic centimeters of blood and a decrease in the erythrocyte count from 9,200,000 to 7,800,000 cells per cubic millimeter.

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1 Minot, G R, and Murphy, W P. Treatment of Pernicious Anemia by a Special Diet, *J A M A* **87** 470 (Aug 14) 1926.

2 Bramwell, B. Anemia and Some of the Diseases of the Blood-Forming Organs and Ductless Glands, Edinburgh, Oliver & Boyd, 1899. Minot, G R, and Forkner, C E. Unpublished Observations.

3 Turk, W. Beiträge zur Kenntnis des Symptomenbildes der Polycythämie mit Milztumor und Zyanose, *Wien klin Wchnschr* **17** 153 and 189, 1904.

Forkner and Scott<sup>4</sup> have recently reevaluated the use of solution of potassium arsenite in leukemia and have shown that its administration to patients with chronic myelogenous leukemia regularly brings about remissions during the earlier course of the disease. The remissions are characterized by reduction of the total leukocyte count to normal or near normal, marked reduction in number, or in some instances complete disappearance, of immature cells from the blood, lessening of the anemia with usually a return to normal of hemoglobin and erythrocyte values, reduction in size of the spleen and of the liver, reduction in the basal metabolic rate and marked subjective improvement. Such remissions can be maintained for several months when the drug is continued in small doses. This treatment for leukemia is purely palliative and comparable to the effects obtained by roentgen or radium irradiation.

There exist certain analogies in the treatment of polycythemia vera and of chronic myelogenous leukemia. Both of these diseases are favorably influenced by intensive treatment with radium or high voltage roentgen rays. The blood picture is at least temporarily improved in each of these diseases by the administration of benzene.

Because of the analogies between the two diseases, it became pertinent to test the effectiveness of the administration of arsenic to patients with polycythemia vera. The effects have been studied in six patients. In each case there has been improvement in the hematologic manifestations, and in five cases the red blood cell and hemoglobin values have returned to or close to normal. The improvement in the state of the blood has been associated with subsidence or disappearance of subjective symptoms. All of the patients have received solution of potassium arsenite by mouth in the amounts indicated on the charts. They have received no other treatment during the course of or immediately preceding the period of study.

#### REPORT OF CASES

CASE 1 (chart 1)—*History*—A 56 year old Irish laborer, whose chief complaint was "skin trouble" of five years' duration, was perfectly well until the gradual onset of skin lesions on the body, chiefly on the legs and trunk. They were described as small, reddish, somewhat elevated itching lesions, varying in size and in the degree of itching produced. Because of the persistence and spreading of the lesions, the patient came to the hospital, where the condition was diagnosed as dermatitis medicamentosa. However, no cause could be found.

4 (a) Forkner, C. E., and Scott, T. F. M. Arsenic as a Therapeutic Agent in Chronic Myelogenous Leukemia. Preliminary Report, J. A. M. A. **97**: 3 (July 4) 1931. (b) Forkner, C. E. The Administration of Solution of Potassium Arsenite in the Treatment of Chronic Myelogenous Leukemia, M. Clin. North America **15**: 1057, 1932.

in the habits or history of the patient. The skin lesions have persisted, although fluctuating in intensity, to the present time.

Three years before admission to the hospital the patient noticed that his face was becoming red, and he considers that the intensity of the color has gradually increased. Also he began to have severe headaches, chiefly vertical and frontal, occurring almost daily and lasting several hours. These headaches gradually decreased in frequency and during the past one and one-half years they have not recurred. It was noticed by the patient about three years ago that a coarse tremor of his arms and hands was developing which has persisted without much change for the last two years. This tremor in itself has not been sufficient to interfere with his activities. The patient has lost about 40 pounds (18.1 Kg) in body weight during the last three years. He believes also that his strength has decreased gradually during this time. Occasional moderate epistaxis occurred during the past three years, but no other tendencies to bleed were noticed.

The family history was not significant and contained no reference to polycythemia, leukemia, anemia, cancer or any familial disease.

The past history was not remarkable.

*Physical Examination*—The following significant findings were revealed on examination: (1) intense deep red color (erythrosis) of the face and skin in general, (2) papular, macular and pustular reddish, slightly scaly, irregular, excoriated skin lesions a few millimeters in diameter scattered over the body, chiefly on the face and extremities, (3) moderately cyanotic mucous membranes, (4) engorged and deep red blood vessels of the retina, (5) rumbling systolic murmur over the apex of the heart, (6) blood pressure, 135 systolic and 85 diastolic, (7) spleen, 4 cm below the costal margin with rounded, smooth edge, and (8) liver, 2 cm below the costal margin, smooth and not tender.

*Laboratory Data*—The urine and stool were not abnormal. The Wassermann reaction of the blood was negative. There were 9,610,000 red blood cells per cubic millimeter and hemoglobin, 169 per cent (26.36 Gm per hundred cubic centimeters of blood). The red blood cells were normal in size and shape. There was no polychromatophilia or stippling. The white blood cells were 13,000 per cubic millimeter.

The differential count of the white blood cells was as follows: polymorphonuclear neutrophils, 80 per cent, polymorphonuclear eosinophils, 4 per cent, neutrophilic metamyelocytes, 2 per cent, small lymphocytes, 6 per cent, intermediate sized lymphocytes, 2 per cent, and monocytes, 6 per cent. The blood platelets were moderately increased in number.

The patient had been observed by other physicians prior to being seen in our clinic, and his blood had remained essentially as recorded for several months before treatment was commenced. During the three weeks immediately preceding therapy we observed him critically and did not note any essential changes either in his clinical condition or in his blood.

Solution of potassium arsenite was administered by mouth in 100 cc of orange juice three times daily immediately after or with meals. The medicine was begun in doses of 5 minims (0.3 cc) three times daily for two days, then increased to 6 minims (0.36 cc) three times daily for two days and subsequently increased in this fashion to 10 minims (0.6 cc) three times daily. Thereafter the dose was increased more slowly, only 1 minim (0.06 cc) per day being added until the patient received 17 minims (1.05 cc) three times daily. The medicine then was decreased by 1 minim per day to 8 minims (0.5 cc) three times daily, on which dose the patient remained for one week. Because the erythrocyte count and hemoglobin

value were not yet normal, the dose was again gradually increased to 18 minims (112 cc) three times daily and thereafter decreased. Medication was then discontinued for two months and another course of treatment followed.

Chart 1 illustrates the effects on the blood cells and also shows the reduction of the basal metabolic rate brought about as the result of treatment. The red blood corpuscles were reduced from 9,610,000 to 4,790,000 per cubic millimeter and the hemoglobin from 169 per cent (26.36 Gm per hundred cubic centimeters of blood) to 95 per cent (14.82 Gm per hundred cubic centimeters of blood).

After the patient had been taking solution of potassium arsenite for three months and was receiving about 50 minims (3.08 cc) daily, there was a rather rapid fall in the number of erythrocytes. This was associated with the appearance of jaundice and with an icteric index of 29 units and a bilirubin of 5.5 mg per hundred cubic centimeters of serum in the blood. The jaundice gradually disap-

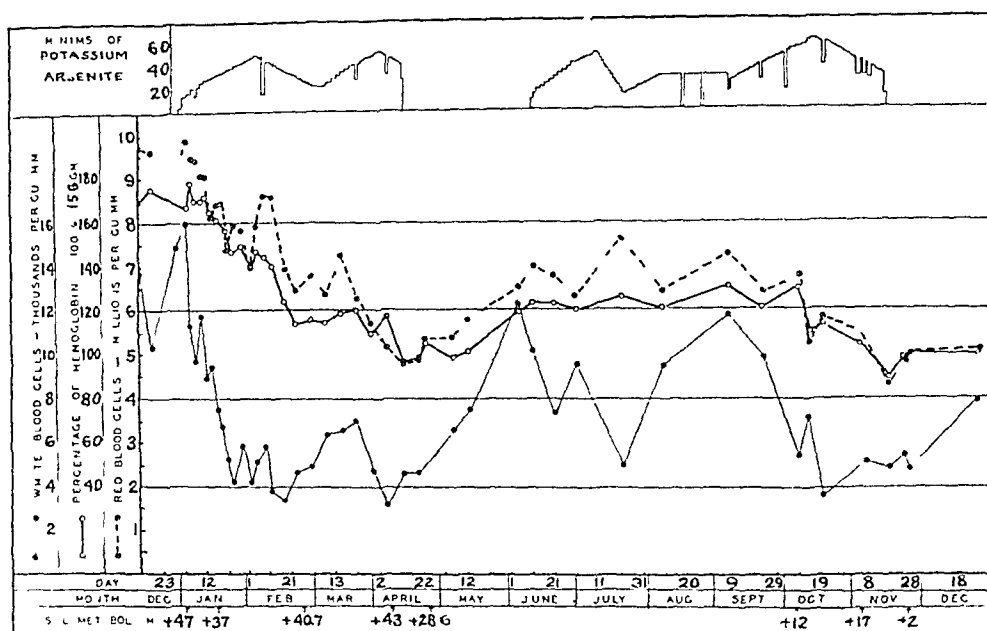


Chart 1—Results of medication in case 1

peared over a period of a few weeks, and presumably was due to increased blood destruction. There was no associated pain, tenderness or increase in size of the liver.

This improvement in the blood was associated with other signs of betterment manifested by moderate decrease in the size of the liver and the spleen, decrease in the intensity of the erythrosis of his skin and mucous membranes, almost complete disappearance of the skin lesions, gain in body weight and strength and subjective improvement.

The other five cases need not be discussed in detail. They represented typical cases of polycythemia vera. Charts 2, 3, 4 and 5 and the table illustrate the effects produced by essentially the same treatment as in the first case. However, there was considerable variation in the amount of solution of potassium arsenite needed to produce the desired result. No other patient required as large doses as did the first one.

CASE 2 (chart 2) —A 67 year old man, who had been known to have had polycythemia vera for at least five years, complained of weakness, nervousness, sleeplessness and attacks of giddiness. Several months prior to coming under our observation he had been treated with phenylhydrazine hydrochloride, 0.1 Gm daily or twice daily, until a total of 3.6 Gm had been taken, which resulted in little improvement either in his blood or in his clinical condition. He had also received intensive treatment with high voltage roentgen rays applied only to the lower extremities. No improvement followed, probably owing to insufficient treatment.

When first seen in our clinic his blood contained 9,190,000 erythrocytes and 21,000 leukocytes per cubic millimeter. The hemoglobin was 133 per cent (20.75

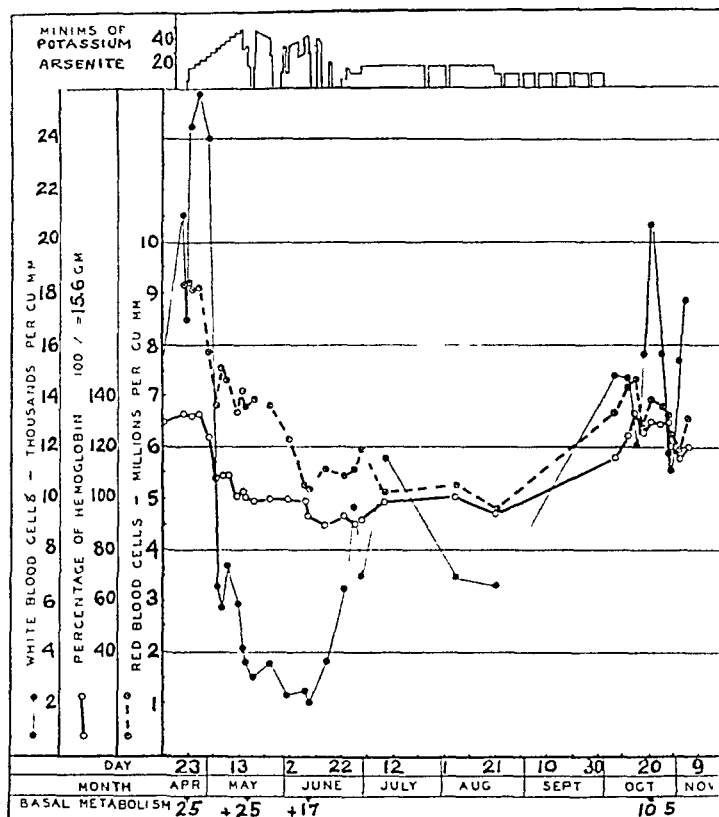


Chart 2—Results of medication in case 2

Gm per hundred cubic centimeters of blood). The hematocrit reading was 69 per cent erythrocytes. As the result of treatment with solution of potassium arsenite the erythrocyte count fell to as low as 4,820,000 cells per cubic millimeter and the hemoglobin to 90 per cent (14.04 Gm per hundred cubic centimeters of blood). The hematocrit reading was reduced to normal (43.2 per cent). The patient became subjectively well, and on small doses of solution of potassium arsenite, from 4 to 5 minims (0.24 to 0.3 cc) three times daily, he remained free of symptoms for about five months. A relapse followed during which his erythrocytes increased to about 7,000,000 per cubic millimeter. The medication was increased (not shown on chart), and another remission was similarly induced.

CASE 3 (chart 3) —A 62 year old Russian Jewish peddler, with polycythemia vera of six years' duration, complained of headache, restlessness, insomnia and

weakness While receiving solution of potassium arsenite his erythrocyte count fell from 7,500,000 to 5,600,000 cells per cubic millimeter and the hemoglobin value from 125 per cent (19.5 Gm per hundred cubic centimeters of blood) to 105 per cent (16.38 Gm per hundred cubic centimeters of blood) Symptomatically, he was moderately improved Several months after omission of the drug the erythrocyte and hemoglobin values again increased, with a return of symptoms

CASE 4 (chart 4) —A 17 year old American schoolboy had polycythemia vera for at least four and one-half years The chief symptoms were headaches, giddiness and pain in the left upper abdominal quadrant His blood contained 8,250,000 erythrocytes and 20,000 leukocytes per cubic millimeter The hemoglobin was 122 per cent (19.03 Gm per hundred cubic centimeters of blood) The hematocrit reading was 63.6 per cent cells The reduction of the erythrocyte and hemoglobin values in this patient were not as prompt or as dramatic as in the others, but when

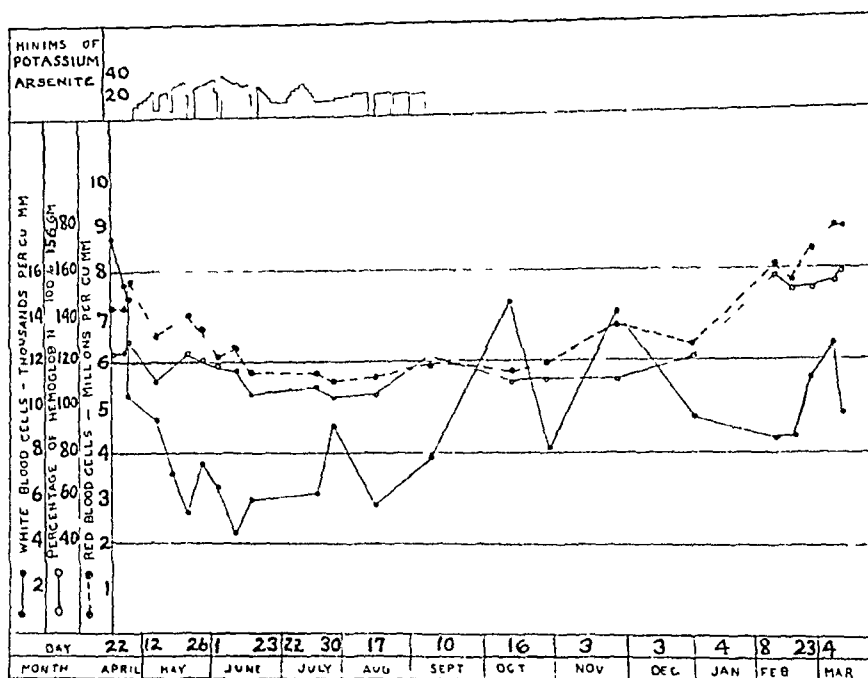
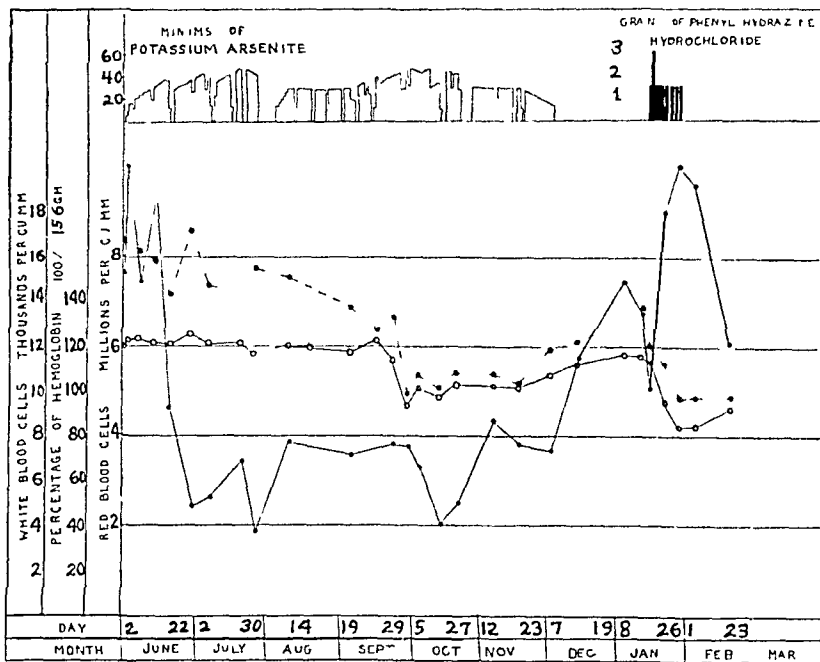


Chart 3—Results of medication in case 3

the medicine was pushed to the full limit of tolerance the red blood cells were reduced to as low as 4,720,000 per cubic millimeter and the hemoglobin to as low as 84 per cent (13.1 Gm per hundred cubic centimeters of blood) The hematocrit reading was reduced to 47 per cent cells

CASE 5—The patient had had polycythemia vera for at least three years He complained of sleeplessness, nervousness, acne and discoloration of the face No treatment had been given for the polycythemia Treatment with solution of potassium arsenite reduced the erythrocyte count from 8,540,000 to 6,665,000 per cubic millimeter, and the hemoglobin from 155 per cent (24.18 Gm per hundred cubic centimeters of blood) to 130 per cent (20.28 Gm per hundred cubic centimeters of blood) in seven weeks The patient, however, seemed to be hypersensitive to the medicine, and it was discontinued before adequate treatment could be carried out

CASE 6 (chart 5) —A 35 year old man had had polycythemia vera for about one year and complained of headache, nervousness and sleeplessness Under treatment



Cart 4—Results of medication in case 4 In this, as in the other charts, ●—●—● represents red blood cells, millions per cubic millimeter, ○—○—○ hemoglobin, percentage, and ●—●—● white blood cells, thousands per cubic millimeter

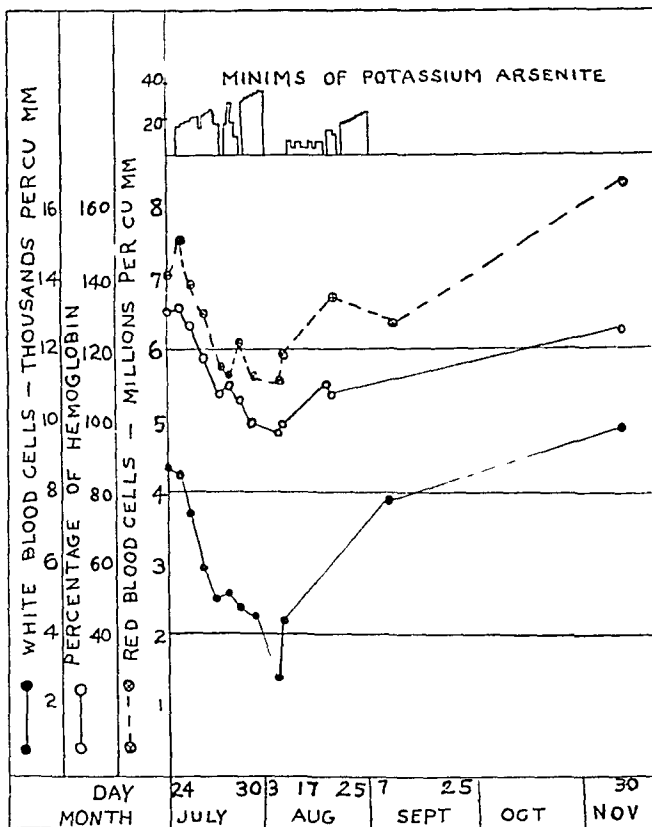


Chart 5—Results of medication in case 6

with solution of potassium arsenite the number of erythrocytes decreased from 7,250,000 to 5,620,000 per cubic millimeter, and the hemoglobin from 131 per cent (20.44 Gm per hundred cubic centimeters of blood) to 98 per cent (15.23 Gm per hundred cubic centimeters of blood). However, this patient was very uncooperative, rarely took the medicine with regularity and eventually was lost sight of altogether. It is seen from chart 5, however, that at the last examination, several months after discontinuing medication, another relapse had occurred.

The accompanying table permits us to make an analysis of the foregoing cases with reference to the time, after the commencement of treatment, when improvement occurred. At the end of ten days after the beginning of medication, in each case there was a decrease in the erythrocytes; the hemoglobin had fallen in four of the cases and usually the leukocytes were fewer.

After twenty days there was in three cases a further significant fall in the number of red blood cells and in the concentration of hemoglobin, and in one of these cases the number of erythrocytes and the hemoglobin value had returned practically to normal. The remaining three cases showed practically no further change until treatment had been continued for a longer time. This lack of uniformity may be explained by variations in the amount of solution of potassium arsenite administered and the precise state of the bone marrow and circulating blood.

After thirty days of treatment the blood remained about the same as after twenty days of treatment, except that as a rule there was greater leukopenia. These facts are illustrated on the charts 1, 2, 3 and 4, where also it may be observed that soon after the commencement of treatment there occurred a significant fall in the number of red blood cells and in the concentration of hemoglobin. Then in five of the six cases no further important decrease in the erythrocyte and hemoglobin values occurred over a period of from ten to thirty days. When the drug was pushed to near the limit of tolerance, the number of erythrocytes and hemoglobin percentage showed a further decrease.

From the table it may be seen that the number of erythrocytes and the percentage of hemoglobin returned practically to normal in one case after twenty days, in two cases after fifty days and in two others only after one hundred and twenty days of treatment. The sixth patient was unable to continue taking the medicine on account of being especially sensitive to it. In each instance the subjective and objective improvement began to appear after about ten days of treatment, when as a rule, the first significant fall in the number of red blood cells and hemoglobin percentage occurred.

Five of the six patients, prior to treatment, had an increased total number of leukocytes in the blood, and all had a greater than normal percentage of polymorphonuclear neutrophils. Mild to moderate



*Effect of Solution of Potassium Arsenite in Polycythemia Vera\**

	Case 1			Case 2			Case 3			Case 4			Case 5			Case 6		
	Red Blood Cells	Hemo- globin	White Blood Cells	Red Blood Cells	Hemo- globin	White Blood Cells	Red Blood Cells	Hemo- globin	White Blood Cells	Red Blood Cells	Hemo- globin	White Blood Cells	Red Blood Cells	Hemo- globin	White Blood Cells	Red Blood Cells	Hemo- globin	White Blood Cells
Prior to treatment	9.61	169	13.00	9.19	133	21.00	7.50	125	17.47	8.25	122	20.00	8.71	155	18.00	7.25	131	8.50
After 10 days of treatment	9.10	170	11.80	7.81	124	24.00	6.63	112	9.45	7.88	121	18.50	7.90	147	16.85	5.75	109	5.00
After 20 days of treatment	7.37	156	5.15	6.68	101	5.95	6.84	118	7.05	7.11	120	9.20	8.01	143	8.60	5.62	100	4.50
After 30 days of treatment	7.01	140	4.20	6.91	99	3.10	6.71	121	7.50	7.37	121	5.20	7.73	153	3.60	5.96	98	1.35
After 50 days of treatment	6.16	114	4.65	5.24	93	2.10	5.81	106	5.90	7.16	121	6.85	6.67	130	5.80			
After 70 days of treatment	6.30	114	6.30	5.99	92	7.00	5.72	109	6.15	7.52	120	7.75	Medication discontinued					
After 90 days of treatment	5.69	109	4.65	5.14	99	11.60	5.70	106	5.60	6.89	117	7.15						
After 120 days of treatment	5.37	98	6.60	4.82	94	6.65	6.05	122	7.75	4.94	93	7.55						

\* The erythrocytes are measured in millions per cubic millimeter, leukocytes in thousands per cubic millimeter, and hemoglobin in per cent (100 per cent = 15.6 Gm per hundred cubic centimeters)

leukopenia occurred in each case as the result of treatment with solution of potassium arsenite. In no instance did the leukopenia decrease below 2,100 white blood cells per cubic millimeter. There occurred no significant change in relative numbers of the different kinds of white blood cells.

In addition to the six cases recorded, Dr. George R. Minot has informed us that he has treated two additional patients, according to the methods we have advised, with entirely satisfactory results.

#### UNTOWARD EFFECTS OF TREATMENT WITH ARSENIC

During the course of treatment of various types of patients with large amounts of solution of potassium arsenite there usually occur some signs or symptoms of toxicity. The character of these effects depends on several factors, chief of which seems to be the susceptibility of different persons to arsenic. Other factors are the quantity of the arsenic ingested with each dose, the amount of dilution of the medicine and the relation of the time of meals to the time of taking the medicine.

Some patients with polycythemia and with leukemia respond to relatively small, and other patients to relatively large, doses of solution of potassium arsenite. We have discovered no explanation for this variability, but it is possible that it may depend on the amount of involvement of the bone marrow.

Loss of appetite and later mild nausea are perhaps the most common early symptoms, indicating that the limit of tolerance for solution of potassium arsenite is being approached, and that if the drug is to be given in larger doses the rate of increase must be gradual. Patients rarely need to vomit as the result of receiving too much of the drug. Vomiting usually indicates that the medicine has been increased too quickly, or that the patients' gastro-intestinal tract is in an unusually irritable state. Diarrhea consisting of from four to six rather loose movements daily is a common symptom when the larger doses of the drug are taken.

Chemosis of the conjunctivae, lasting a few days, occurred in two of our six patients with polycythemia vera and was a troublesome, but not a serious complication.

Slight burning sensations in the toes and fingers occur occasionally in patients under treatment with solution of potassium arsenite, but no permanent changes associated with these sensations have been observed.

Peripheral neuritis is said to follow administration of arsenic in rare instances. We have not observed this complication in the treatment in the cases reported in this paper or in the treatment of about thirty other patients with other diseases.

Herpes zoster along the course of the sixth left intercostal nerve occurred in the second case reported, but not during the period of observation shown on the chart. This patient had received solution of potassium arsenite almost continuously over a period of five and one-half months. It was then discontinued for three months and resumed, but owing to a misunderstanding the patient received the medicine much too rapidly. In the course of six days the dose had been increased from 15 to 35 minims (0.92 to 2.16 cc.) daily and then was decreased to 21 minims (1.31 cc.) daily. It was on the ninth day following the beginning of this second course of treatment that the herpes zoster occurred. In a total of thirty-five cases, representing various diseases, particularly leukemia, we have noted, during treatment with solution of potassium arsenite, herpes zoster to develop in five, an incidence of 14.3 per cent. This is possibly a somewhat higher incidence than is to be expected in similar cases under other forms of treatment. Owing to misunderstood orders, four of the five patients in whom herpes zoster developed received the drug in a grossly irregular manner or in too rapidly increasing amounts. The herpes zoster took the usual course, and in no instance has it left any permanent damage.

Pigmentation of the skin and hyperkeratosis have been reported following in the wake of long-continued treatment with solution of potassium arsenite. In two of the cases reported in this paper, in one instance after five and one-half months, and in the other after ten months of almost continuous medication, some slight thickening and drying of the skin of the palms of the hands and soles of the feet developed which persisted for a few weeks and then entirely disappeared after the arsenic temporarily had been omitted.

In one of the patients with polycythemia vera mild transient jaundice developed at the time when the red blood cells were decreasing rapidly, presumably due to destruction of the cells. It is possible that this jaundice could have been due to liver damage, but this seems unlikely in view of the fact that jaundice has not occurred in any of the patients with chronic leukemia whom we have treated, some of whom have received large doses of solution of potassium arsenite continuously for as long as nine months.

#### METHOD OF ADMINISTERING SOLUTION OF POTASSIUM ARSENITE

From our experience we feel that the best results can be obtained by adhering to the rules given here. In a previous publication<sup>4b</sup> it was suggested that the first dose should be about 5 minims of solution of potassium arsenite three times daily. We are now of the opinion that beginning doses of 3 or 4 minims (0.18 or 0.24 cc.) three times daily are somewhat better borne at the start and produce as satisfactory

results This initial dose is continued for two days, and then the total daily dose is increased by 3 minims This amount is given for two days Thereafter the dose is increased at the same rate until the first sign of intoxication, anorexia, is noted This sign, as a rule, is first noticed when the dose reaches about 24 minims (1.48 cc) daily When this dose of 8 or 10 minims three times daily has been reached, or earlier if indicated, the subsequent increments in amounts of the drug must be added more slowly at the rate of an increase of not more than 1 minim to the total daily dose By such a method medication may be carried up to 12, 15 or even 20 minims (0.74, 0.92 or 1.25 cc) three times daily

The policy we have found of most value is to continue increasing the medicine until desired effects are obtained or until the limit of tolerance has been reached Frequently, the best therapeutic results are to be obtained with the dose which is near the upper limit of tolerance With solution of potassium arsenite, as with many other drugs, the tendency is to give too little rather than too much Mild toxic symptoms are to be disregarded, or the best results often will not be obtained

When the blood has improved considerably or when the limit of tolerance has been reached, the solution of potassium arsenite gradually should be withdrawn The total daily dose may be decreased by 1 minim daily until the patient is taking about 5 minims three times daily, which amount may be continued without harm for at least several months If, with the larger doses, rather severe toxic symptoms develop, the drug may be entirely omitted for forty-eight or seventy-two hours and then resumed in doses equivalent to about three fourths or two thirds of the amount which the patient was taking at the time of the development of the symptoms From this point the drug may again be increased or may be decreased as indicated by the effects on the patient

The medicine is best given either with or immediately after meals well diluted in orange or tomato juice or some other flavored drink

#### COMPARISON OF THE USE OF SOLUTION OF POTASSIUM ARSENITE WITH OTHER METHODS OF TREATING POLYCYTHEMIA VERA

There exist essentially three methods of treatment of polycythemia vera (1) venesection at intervals, (2) administration of phenylhydrazine, usually as hydrochloride and (3) irradiation by means of radium or high-voltage roentgen rays No other methods have been shown to be of any distinct value None of the foregoing methods are curative The first is of very transient value and is wrong in principle in that the removal of blood acts as a stimulus for new blood formation

The administration of phenylhydrazine is frequently effective in reducing the polycythemic aspects of the disease, but it is a drug which must be given with extreme care because of its cumulative and frequently delayed action. Thromboses of blood vessels occur frequently following treatment with phenylhydrazine, more frequently than with any other treatment.<sup>5</sup> Phenylhydrazine improves the blood of the polycythemic patient by destruction of red blood cells and does not in any way produce a more normal formation of blood. The third method of treatment, that of irradiation, has as its purpose the inhibition of the abnormal function of the bone marrow.

Although, in the absence of any knowledge as to the etiologic agent it is impossible to discuss with certainty the rationale of any form of therapy, this later method of irradiation appears to be more logical and of more prolonged value than the other two methods, providing an adequate amount of treatment is skillfully given.

Arsenic in the form of solution of potassium arsenite appears to act chiefly to depress the activity of the bone marrow,<sup>6</sup> but at the same time in large doses it perhaps may hasten the destruction of erythrocytes.

From the study of these six cases of polycythemia vera and of two additional cases observed by Dr. George R. Minot, it is suggested that the administration of solution of potassium arsenite is a safe and reliable method, which may be used alone or in conjunction with other methods for the palliative treatment of polycythemia vera.

#### SUMMARY AND CONCLUSIONS

1 Six patients with polycythemia vera have been treated by the oral administration of relatively large doses of solution of potassium arsenite.

2 Distinct improvement in the clinical and hematologic manifestations has occurred in each patient in from twenty to fifty days.

3 The induced remissions were characterized by reduction of the erythrocyte, hemoglobin and hematocrit values to normal or nearly normal, reduction of the basal metabolic rate to normal, increase in body weight, increase in strength and subsidence or disappearance of symptoms.

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5 Giffin, H. Z., and Conner, H. M. The Untoward Effects of Treatment by Phenylhydrazine Hydrochloride, *J. A. M. A.* **92** 1505 (May 4) 1929.

6 Stockman, R., and Charteris, F. J. The Action of Arsenic on the Bone Marrow of Man and Animals, *J. Path. & Bact.* **8** 443, 1903. Isaacs, R. The Effect of Arsenic on the Maturation of Red Blood Cells, *Folia haemat.* **37** 391, 1928. Farley, D. L. Depressed Bone Marrow Function from the Arsphenamines, *Am. J. M. Sc.* **179** 214, 1930. Forkner and Scott.<sup>4a</sup>

4 The remissions may be prolonged at least for several months by continuation of the medication in reduced amounts

5 The method of administration of the drug and the untoward effects due to treatment with arsenic are discussed

6 The administration of solution of potassium arsenite to patients suffering from polycythemia vera constitutes a safe and reliable method for the palliative treatment of this disease

# DIAGNOSIS OF OBSCURE CASES OF PERNICIOUS ANEMIA

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Occasions frequently arise when it is extremely difficult to make a diagnosis of pernicious anemia with absolute certainty. This difficulty has been enhanced since the discovery of the efficacy of liver<sup>1</sup> and other potent materials<sup>2</sup> because of the widespread tendency of physicians, before making every effort to reach a definite diagnosis, to treat all patients with anemia, and often patients with vague neurologic disturbances, as if they had pernicious anemia. The premature feeding of potent material will often so mask the natural course of the disease and the typical morphologic changes in the blood that two of the most valuable diagnostic aids will be lost.

The result of this tendency to treat anemic patients as patients with pernicious anemia naturally leads to a certain degree of uncertainty on the part of both patient and doctor, so that ultimately the treatment will be carried out half-heartedly, and the patient will thereby be subjected to the danger of development of neurologic symptoms because of inadequate therapy, or to unnecessary expense if the diagnosis is incorrect.

It is becoming more and more apparent that if patients are adequately treated and the blood maintained at a normal level, lesions of the spinal cord will develop in few, if any, of them<sup>3</sup>. There is likewise

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From the Medical Clinic, the School of Medicine, Johns Hopkins University and Hospital

1 Minot, G R, and Murphy, W P. Treatment of Pernicious Anemia by a Special Diet, *J A M A* **87** 470 (Aug 14) 1926

2 Sturgis, C C, and Isaacs, R. Desiccated Stomach in the Treatment of Pernicious Anemia, *J A M A* **93** 747 (Sept 7) 1929. McCann, W S. Effect of Kidney on Blood Regeneration in Pernicious Anemia, *Proc Soc Exper Biol & Med* **15** 255, 1928. Ungley, C C. Effect of Brain Diet in Pernicious Anemia, *Lancet* **2** 63, 1931, *ibid* **1** 227, 1932

3 (a) Ungley, C C, and Susman, M M. Subacute Combined Degeneration of the Cord. Symptomatology and Effect of Liver Therapy, *Brain* **52** 271, 1929. (b) Baker, B M, Jr, Bordley, J, III, and Longcope, W T. The Effect of Liver and Liver Extract upon the Symptoms and Signs Referable to the Nervous System in Pernicious Anemia, *Am J M Sc* **184** 1, 1932. (c) Richardson, W. Pernicious Anemia (Results of Treatment with Liver or Its Derivatives in 67 Cases), *New England J Med* **200** 540, 1929

increasing evidence that if patients with changes in the cord are treated vigorously, many may have reasonable hope of improvement<sup>3b</sup> Inasmuch as it often takes months or even years for signs of this improvement to appear, it is obvious that the discomfort and expense of taking massive amounts of potent material over such a long period is unwarranted unless an absolute diagnosis has been made

To make a diagnosis of pernicious anemia is, as a rule, relatively simple, but occasionally it is necessary to resort to a therapeutic test This entails a control period without treatment, followed by the administration of large amounts of potent material, with daily counts of the reticulocytes and of the red blood cells and an estimation of hemoglobin Should the response of the blood be inhibited by infections, arteriosclerosis or chronic diseases of another nature,<sup>4</sup> an absolute diagnosis by this method may not be possible on account of an inadequate rise in reticulocytes and red blood cells It is not uncommon, furthermore, to encounter patients with neurologic disturbances who have relatively little alteration in the morphology of the blood When there is only moderate anemia, the examination of the blood smear may leave considerable room for doubt as to the diagnosis In the majority of cases measurement of the mean volume of the red blood cells reveals a macrocytosis even when the anemia is slight,<sup>5</sup> and when this is associated with bilirubinemia and urobilinuria in a patient whose symptoms and signs suggest pernicious anemia, the latter is the likely diagnosis Not only is it true, however, that in rare instances even these signs may be absent, but it must also be kept in mind that the discovery of macrocytic anemia in itself does not always signify pernicious anemia Some instances have been observed in which signs and symptoms of disease of the spinal cord have occurred in association with macrocytic anemia in the absence of pernicious anemia<sup>6</sup>

The diagnosis may be even more difficult in instances in which the patient has been receiving small amounts of potent material before coming under observation, as a result, the blood picture may so nearly approach normal that pernicious anemia will seem unlikely, and the patient will be discharged untreated If, however, pernicious anemia is suspected, treatment with liver may be discontinued for purposes of diagnosis to ascertain whether or not the blood changes to the typical

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4 Beebe, R T, and Lewis, G E The Maintenance Dose of Potent Material in Pernicious Anemia, *Am J M Sc* **181** 796, 1931

5 Wintrobe, M M Hemoglobin Content, Volume and Thickness of the Red Blood Corpuscle in Pernicious Anemia and Sprue, and the Changes Associated with Liver Therapy, *Am J M Sc* **181** 217, 1931 Wintrobe, M M The Size and Hemoglobin Content of the Erythrocyte, *J Lab & Clin Med* **17** 899, 1932

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picture of the disease. This procedure is dangerous and time-consuming, however, for the blood may change very slowly, while changes in the coïd may advance rapidly, just when the most vigorous therapy with potent material is indicated.

We recently encountered two cases which offered so much difficulty in diagnosis that it seemed necessary to resort to a special method of examination. Castle<sup>7</sup> showed that hamburger steak properly digested with normal gastric juice contains a substance capable of causing a remission in pernicious anemia. We employed this method for diagnostic purposes. Hamburger steak was digested with the gastric juice of the patients in question and given to two patients suffering from pernicious anemia who were having a relapse. The effect of this feeding was compared with that produced by giving hamburger steak digested with normal gastric juice.

#### METHOD

The patients to be treated were given 0.5 mg. of histamine sulphate subcutaneously every morning. The fasting stomach contents were then collected by means of a nasal catheter. The stomach excretion was small, but, by repeated aspiration, in the course of an hour from 50 to 75 cc. of gastric juice could be collected. Two hundred grams of hamburger steak, to which 4 Gm. of commercial pepsin had been added, was then brought by the addition of 2/3 concentrated hydrochloric acid to a  $p_H$  of 4.4. This end-point was determined by the pink color produced by the addition of a drop of the mixture to a drop of alizarin monosodium sulphonate solution. The mixture was then digested for two hours at 37 C. By the addition of concentrated sodium hydroxide the  $p_H$  was then lowered to 7.0, at which point the addition of a drop of the mixture causes bromthymol blue to become green. Seventy-five cubic centimeters of the gastric juice to be tested was added and allowed to incubate for two hours. It was then strained through a fine mesh sieve and given on six successive days by a nasal tube to a patient known to have pernicious anemia. The patients suffering from pernicious anemia who were to receive the mixture to be tested were first observed without treatment for a period of two weeks, in order to determine whether or not their blood remained at a stationary level. During this time reticulocytes were counted daily, and red cells and hemoglobin were determined twice a week. Patients with erythrocyte counts of less than 3,000,000 were selected as recipients of the mixture of hamburger steak and gastric juice, in order that a significant response of the reticulocytes and a rise in the blood count might be obtained. Ten or more days were allowed to elapse between the administration of the mixture to be tested and the material known to contain the intrinsic factor.

#### REPORT OF CASES

CASE 1—A white man, aged 44, was admitted to the Johns Hopkins Hospital on Sept. 22, 1930. The history, physical findings and results of examination of blood were compatible with pernicious anemia, except for the presence of a small amount of free hydrochloric acid in the gastric contents. Following the oral

<sup>7</sup> Castle, W. B. Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, *Am. J. M. Sc.* **178**: 748, 1929.

administration of liver extract in large doses, the reticulocyte peak was only 48 per cent, although the red blood cells were 1,860,000. The blood later showed some improvement, but for two years the red cells did not rise above 2,500,000, in spite of the fact that the patient daily took the extract derived from 400 Gm of liver. At this period he had a severe attack of phlebitis migrans, which left him with brawny edema of both legs, persistent fever and leukocytosis. This was followed by the gradual onset of changes in the spinal cord.

We felt that the diagnosis of pernicious anemia was warranted, and in view of the poor response to liver, it seemed necessary to give the patient massive amounts of potent material. Our plan was to give as much as 10 vials of liver extract no. 343 daily for one year. In view, however, of the presence of free hydrochloric acid in the gastric juice, the fever, leukocytosis, atypical response of the blood to feeding of liver and absence of papillary atrophy of the tongue, it seemed inadvisable to go to the trouble and expense of massive feeding unless the diagnosis of pernicious anemia could be definitely established. A section of sternal bone marrow was examined but was not found to be particularly abnormal.

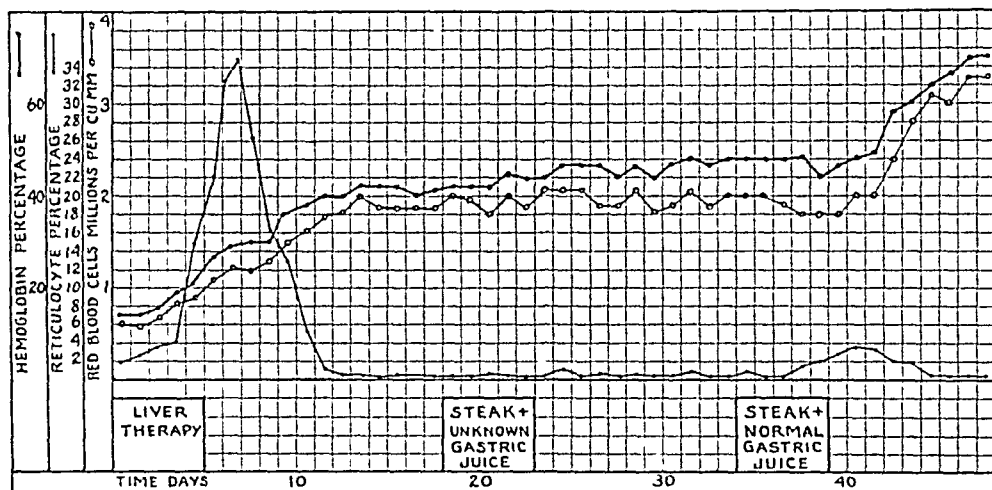


Chart 1—Because of the extreme grade of anemia, this patient was first given sufficient liver extract to eliminate the danger. After an adequate delay, hamburger steak digested with the unknown gastric juice was administered. The ineffectiveness of this gastric juice is apparent when the lack of any change in the blood is compared with the small but definite rise in reticulocytes and the increase in red cells and in hemoglobin which followed the feeding of hamburger steak and normal gastric juice.

The patient's gastric juice was then tested by the method described, and was found to be inert as compared with the definite response obtained when the same amount of normal gastric juice was used in a similar manner (chart 1).

The subsequent course of the disease in this patient has proved beyond doubt that he is suffering from pernicious anemia. Intensive therapy for two years has maintained his blood at a normal level, and degeneration of the cord has not advanced.

The second case is of such interest that the history will be given in detail.

CASE 2—*History*—A white man, aged 45, a university graduate, had been a good student. Until the illness under discussion began, he was considered a very intelligent man. His father died of paralysis at 45 years, but further details of

the illness could not be elicited. His mother died at 36 of pernicious anemia. One sister had some form of paralysis from which she recovered. Two sisters and one brother were living and well.

The patient's previous health had been excellent, with no illness of importance. He had been athletic and was a good tennis and handball player.

The present illness began about seven years before admission, when he noticed for the first time a tendency to easy fatigability. He began to lose his accuracy in tennis and handball. In the few years which followed he had many financial worries, he became nervous and tired. He had periods lasting several months when symptoms of fatigability and nervousness were much more apparent. During this time, however, he noticed no pallor, but gained weight and therefore eliminated from his diet milk, fat, cream, potatoes and bread.

Eighteen months before admission he became aware for the first time of numbness in his hands, which caused difficulty in writing. This was soon followed by such unsteadiness in his legs that it was necessary to discontinue his athletics.

Twelve months before admission his walking became much worse, he grew very unsteady, and his friends were aware of a diminution in his mental acumen. He saw his family physician, who reported that his blood was not particularly abnormal, but in view of the neurologic disturbances prescribed liver, which the patient took for two months. He then discontinued it, because he noticed no improvement.

Nine months before admission he was seen by a competent neurologist, who reported the following abnormalities. The tongue was slightly smooth, but not red. The cranial nerves were normal. There was no weakness or tremor. There was slight error in the finger to nose test, and the gait was slightly unsteady. The patient could not walk heel to toe, but the gait was spastic, not ataxic. There was numbness up to the wrists and the hips, cutaneous sensibility in this region was altered but not lost. Sense of passive movement and position of fingers and toes was diminished or lost. There was loss of two-point sense in the hands and loss of vibratory sense in the legs and slightly in the hands. The reflexes were slightly sluggish in the arms, but active in the legs. There was no clonus. The plantar and abdominal reflexes were sluggish. The reaction to the Wassermann test was negative. Roentgenograms of the gastro-intestinal tract showed no abnormalities. Gastric analysis showed no free hydrochloric acid and a total acid of 6 degrees. The red blood cells numbered 5,000,000, the hemoglobin was 100 per cent (14.5 Gm), the white blood cells, 7,000, and the smear, normal.

The impression of the neurologist was that the condition was pernicious anemia, but because of the normal blood, he changed the diagnosis to multiple sclerosis, evidently overlooking the fact that the patient had been taking some liver for about three months before the examination was made.

The patient discontinued the liver nine months before admission, and for several weeks felt a great deal better. He improved to the point of being able to play tennis again, and his voice, which had become somewhat unsteady, became stronger.

Suddenly the disease began to advance rapidly. Spasticity progressed to the point of confining him to bed, his hands became very unsteady, and for the three months preceding admission he was unable to walk or write.

He was admitted for short periods to two other hospitals. In one he was thought to have multiple sclerosis, and was treated with a vaccine, and in the other he was thought to have pernicious anemia and was therefore treated with liver in small amounts for several weeks, without improvement. He was admitted to the Johns Hopkins Hospital on Jan 21, 1932.

*Examination*—On admission, the temperature was 99 F, the pulse rate, 80, the respiration, 22, and the blood pressure 120 systolic and 80 diastolic. The patient was well nourished and cheerful, almost euphoric at times, and seemingly without insight into his condition. This mental change had been noted by the family during the year previous to presentation. Because of the great spasticity and contractures of his legs, he had become completely bedridden. There was a large amount of soft, flabby, subcutaneous fat, and the skin had a slightly yellowish color. The hair was prematurely gray. The mucous membranes showed slight pallor. The pupils and extra-ocular movements were normal. The fundi showed no definite abnormalities, except slight pallor on the temporal side of the left disk. Visual fields and visual acuity were normal. The retinal vessels were normal. The tongue was rather large and red, with slight but definite atrophy of the papillae at the tip and along the margin. The thyroid was just palpable. The heart and lungs were normal. No sclerosis of the peripheral vessels was evident. There were no palpable abdominal masses, and no edema or clubbing of the extremities.

Speech was at times a little slurred. The only demonstrable involvement of the cranial nerve was some deviation of the soft palate to the right on phonation, and absence of the gag reflex. There was diminution in the sense of pain below the third rib on both sides. This sense was practically absent below the twelfth dorsal vertebra on the right and the first lumbar on the left. Light touch could not be felt below the sixth dorsal vertebra. Vibratory sense was absent in the legs and spine up to the first dorsal vertebra and absent over both wrists and the right elbow. Sense of passive movement and position was lost in the fingers and toes, and diminished in the shoulders and elbows. There was slight weakness of all muscle groups of the arms, marked ataxia on the finger to nose and finger to finger tests, and marked adiadokokinesis, worse in the left hand than in the right. The legs were very spastic, with contractures, especially of the hamstrings on the left. Coordination could not be tested because of the contractures. There was no fibrillary twitching or muscular atrophy. All the deep reflexes were hyperactive, more so in the legs than in the arms. There were bilateral Babinski and Hoffmann signs. The abdominal reflexes were absent. Gait and station could not be tested, because the patient could neither stand nor walk. There was occasional loss of vesical and rectal sphincter control during the last months.

*Laboratory Findings*—The urine was normal, urobilinuria was absent. Examination of the blood showed red blood cells, 5,020,000, hemoglobin, 92 per cent (13.3 Gm), white cells, 6,200, polymorphonuclears, 62 per cent, polymorphonuclear eosinophils, 1 per cent, polymorphonuclear basophils, 0.5 per cent, color index, 0.92, reticulocytes, 0.9 per cent, lymphocytes, 33.5 per cent, and monocytes, 3 per cent.

The smear showed moderate anisocytosis, with a number of macrocytes and rather numerous microcytes. One polychromatophilic cell was seen. The mean corpuscular volume was 83 cubic microns. Platelets were plentiful.

The Wassermann tests of the blood and the spinal fluid were negative. The Pandy and colloidal mastic tests also gave negative results. Gastric analysis after fasting showed free hydrochloric acid, 0, total acid, 7.5 degrees, the histamine test (0.5 mg subcutaneously) revealed free hydrochloric acid, 0, and total acid, 2.5 degrees. The van den Bergh test of the blood showed an indirect trace. The icteric index was 12.

It was important to reach an accurate diagnosis in this case. In the first place, had it been possible to make a diagnosis of pernicious anemia a year previously, with proper treatment the patient might not have reached such a state of hopeless invalidism. Furthermore, since it is becoming increasingly evident that

the only way in which improvement, or at least the prevention of further advance of symptoms in the cord, can be expected is by the administration of massive amounts of potent material, our problem was to determine whether or not this patient should be subjected to the expense of such treatment

As a final diagnostic proof, therefore, the gastric juice was tested as described in the preceding paragraphs. It was found to be impotent as compared to the control normal juice (chart 2)

With these data in hand it seemed logical to treat him vigorously, not that much improvement could be expected in such an advanced and long-standing case, but in the hope of preventing further progress of the disease. He was therefore given as much liver as he could take, which amounted to 500 Gm of raw liver emulsion daily, and in addition 600 cc of domestic liver extract made according to Castle's formula<sup>8</sup>

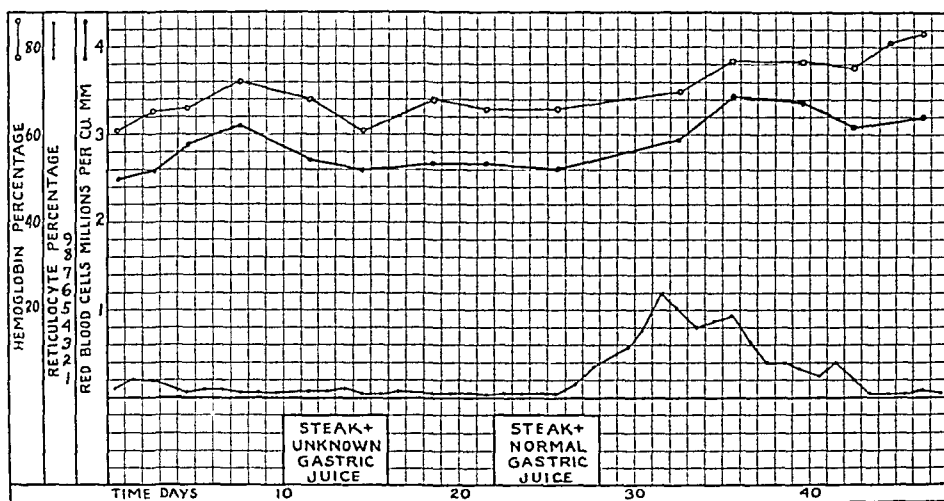


Chart 2—No response of reticulocytes, red blood cells or hemoglobin followed administration of hamburger steak digested with unknown gastric juice. Good response of reticulocytes and rise in red blood cells and hemoglobin followed the feeding of normal gastric juice and hamburger steak.

As was expected, no rise in reticulocytes was obtained because of the high level of red blood cells and hemoglobin. The latter elements rose somewhat, and the patient soon felt and looked a great deal better.

The feeding of massive amounts of liver has been continued for six months. Although there is as yet no demonstrable improvement in the signs and symptoms due to the lesions of the nervous system, there has been no advance of the disease.

#### COMMENT

A question which arises at once is whether the absence of the "intrinsic factor" is confined to cases of pernicious anemia. Exhaustive studies on this subject have not been carried out. Castle reports

<sup>8</sup> Castle, W. B., and Bowie, M. A. A Domestic Liver Extract for Use in Pernicious Anemia, *J. A. M. A.* 92:1830 (June 1) 1929.

that the gastric juice of patients suffering from idiopathic, microcytic anemia is effective in producing a reticulocyte response in pernicious anemia<sup>9</sup>

Whatever observations may show in other conditions, there seems to be sufficient evidence at present to believe that in a patient whose signs and symptoms suggest pernicious anemia the discovery of the absence of the intrinsic factor in the gastric juice makes the diagnosis of pernicious anemia at least extremely probable

#### SUMMARY AND CONCLUSIONS

Two cases are described in which it was not possible to make an absolute diagnosis of pernicious anemia by the usual methods of examination

Castle's discovery of the efficacy of hamburger steak digested with gastric juice from normal persons in producing a remission in pernicious anemia was utilized to establish the diagnosis in these cases

This was done by comparing the effectiveness of the gastric juice obtained from the patients in question with that of gastric juice from normal persons when fed to patients suffering from pernicious anemia

Such a test is of assistance in confirming the diagnosis (1) when, on account of infection, chronic disease of any nature and arteriosclerosis, the response to appropriate treatment is inadequate and leaves room for doubt as to diagnosis, (2) in cases of damage to the spinal cord and little or no anemia, when an absolute diagnosis cannot be made on the basis of the morphology of the blood or therapeutic tests, and (3) in patients with little anemia who are already receiving liver therapy and in whom cessation of treatment for the purpose of diagnosis might prove harmful and permit onset or advance of the damage of the spinal cord

The importance of making a definite diagnosis early in the disease is emphasized, particularly in patients suffering from involvement of the central nervous system. In such cases, if the diagnosis is definitely established, vigorous therapy can be continued for many years, with the full confidence of both the patient and the physician that the diagnosis is correct, and that time and effort are not being wasted in treatment

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9 Castle, W. B., Heath, C. W., and Strauss, M. B. Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia, *Am. J. M. Sc.* 182:741, 1931

## Book Reviews

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**Entstehung, Erkennung und Behandlung innerer Krankheiten** By Ludolf Krehl Volume 3 Price, 18 marks Pp 289 Berlin F C W Vogel, 1933

It is impossible to review this book without considering its two companions, the first on pathologic physiology and the second on diagnosis. It is equally impossible to review the trilogy without reflecting on the author and on his peculiar aptitude for writing a complete textbook of medicine in the form he has selected.

Professor Krehl was born in 1861, and became a doctor of medicine when he was 25 years old. Subsequently he acquired an admirable medical training first as Privat Dozent in Leipzig, then as professor of medicine at Jena—receiving the honor when he was only 31 years old—then as Professor at Marburg, Greifswald, Tübingen, Strassburg and finally Heidelberg. With an experience of such breadth, it is no wonder that Sir William Osler remarked of him in a preface to Hewlitt's second edition of the translation of the "Pathological Physiology" published in 1907, "The author has had the advantage of prolonged laboratory training to which has been added that accurate knowledge of disease to be had only by years of study and teaching in the wards."

The present volume may be said to owe its origin to a little book which first appeared in 1893 under the title of "Grundriss der allgemeinen klinische Pathologie." In 1898, its name was changed to the better known one of "Pathologische Physiologie," and ever since it has enjoyed a well deserved popularity. The thirteenth edition was published in 1930 as the first part of a new medical textbook, and was received with so much enthusiasm that a fourteenth edition was necessary in 1932. This section of the textbook has already been reviewed in the ARCHIVES, and can be recommended with unstinted enthusiasm to every one.

The second part of the series, on diagnosis, was off the press in 1931, and required a second edition in 1932. This section, too, has been reviewed in the ARCHIVES. The review speaks well of the volume and comments on the fact that it is obviously and refreshingly written by a single author, who thinks as he writes, is inclined to philosophize in an engaging manner on various medical trends as he has seen them develop in his experience and, above all, stresses the point of view that the good physician must strive continually to apply to the patient as an individual sample of humanity what is known of the science of medicine.

The third section, on treatment, has just appeared, and is in every way up to the standard of the rest of the series. As might be expected of a writer of the author's training, it is comparatively short—289 pages against 716 pages on pathologic physiology and 192 pages on diagnosis. As is stated in the preface, it is not written for professors or men of that caliber, but for young German practitioners who are beginning. The general principles of treatment are well covered, as are the various forms of treatment to be used in ameliorating the symptoms of disease involving the special systems. Different kinds of treatment are discussed, such as the use of drugs, of surgery, of massage and of radiotherapy, hydrotherapy and psychotherapy. An admirable bibliography is appended to nearly every page, and almost all the references are to German writers. Presumably this is done by intention, since the book is written for the benefit of young German physicians who may be expected to read the German literature but who are less likely to read French or English easily.

The most appealing feature of Professor Krehl's book, however, regarding the three books as a single unit, lies in the fact that it is written by one man and from an individualistic point of view. It has been said that the rapid growth of medical knowledge during the last few years has made it almost impossible for a single person to master the entire field, and that the age of specialism has arrived. Professor Krehl refutes this argument. He has written a book which

covers the entire field of medicine, and which demonstrates a comprehensive knowledge of the subject. He expresses his personal views on all phases of medicine with clearness and force. He writes delightfully, so that the book as a whole moves along without bumps or jerkiness. He seems to have reaccomplished today what Niemeyer accomplished for German medical literature in 1858. Perhaps his example will inspire one of our modern American authors to make as equally a valuable contribution to the American medical literature as did Osler in 1892.

**Lectures on Endocrinology** By Walter Timme, M D, Senior Attending Neurologist, Neurological Institute, New York, Professor of Clinical Neurology, Columbia University (College of Physicians and Surgeons), Past President, Association for the Study of Internal Secretions and Association for Research in Nervous and Mental Diseases. Second edition. Price, \$2 50. Pp 192, with 38 illustrations. New York: Paul B Hoeber, Inc., 1932.

In a rambling account, woefully antiquated, the author considers rather unscientifically the following glands, thymus, thyroid, pineal, parathyroid, suprarenal and pituitary glands and the gonads. For example "Theoretically, the thymus secretes a substance which has vagotonic properties, ammonium carbonate being converted finally into urea by parathyroid action." In the short section on hyperparathyroidism appears a final paragraph in which the author refers to the administration of parathyroid extracts, whereas in the first paragraph such administration is obviously contraindicated, since osteitis fibrosa cystica is shown to be due to a hypersecretion of the parathyroid glands. Such important topics as homeostasis and the tuberal syndrome are not even mentioned. Pitressin and pitocin are referred to as vasopressin and oxytocin—names long ago discarded. The recent interesting work on hebin is not even referred to, neither did the reviewer find a discussion of theelin, theelin, progestin or the purified preparations of the male sex hormone. There is little justification for a book of this type.

**Anleitung zur fruhzeitigen Erkennung der Krebskrankheit** By Best, Fromme, Payr, Rostoski, Saupe, Schmorl, Tonndorf and Warnekros. Second edition. Price, 3 marks. Pp 134. Leipzig: S Hirzel, 1932.

The first edition of this book was published in 1917. Very few copies came to this country, so that it is almost unknown here. It was written for the benefit of general practitioners not in a position to be especially familiar with cancer, and endeavored to give them easily digested information on the various ramifications of this subject. While it did not differ greatly from other books written for the same purpose and published in other parts of Europe at about that time, yet it was unusually comprehensive, well put together by a group of able writers, and did not contain information unsupported by known facts.

The second edition of the book has the same purpose and is written in much the same style. It has grown in size to keep abreast of the progress that has been achieved in the last fifteen years and so is forty pages longer. Several of the original authors have been changed, and now, with but one exception, they all come from Dresden. They write well and clearly.

In brief, the book gives an admirable summary of the various methods at present available for the early recognition and treatment of cancer. It is written simply and contains so much information on cancer of practical clinical value that, without doubt, the book will be of considerable use to the practitioners for whose benefit it has been written.

**The Laboratory in Surgical Practice** By E C Dodds, M V O, M D, and Lionel E H Whitby, C V O, M D (Camb), M R C P (Lond) D P H. Price, 8 shillings, 6 pence, net. Pp 196. London: Constable & Co, Ltd, 1931.

This is a book that every practitioner of surgery or medicine would profit greatly by reading, if he has the patience to do so. Because of the nature of the



subject, it becomes laborious to read it through completely, hence, it must resolve itself in becoming a reference book, and, as such, it is excellent for the practitioner

It is not sufficiently exhaustive for the pathologist or the laboratory man. It does coordinate the laboratory findings with the clinical picture and shows or reminds the clinician what future laboratory examinations should be made when certain pathologic changes are suspected, and how these findings should be interpreted

Much of the first half of the book is given over to subjects that fall almost entirely within the realm of the clinical pathologist, but in the chapters on the kidney, stomach, gallbladder and liver and the thyroid gland, the authors, I believe, reached the objective of the book in making it a helpful laboratory manual for the surgeon. It is a valuable addition to any library

**An Index of Prognosis and End-Results of Treatment** By Various Writers  
 Edited by A. Rendle Short Fourth edition, fully revised Price, \$12  
 Pp 599 New York William Wood & Company, 1932

The fourth edition of this book appears ten years after the one that immediately antedated it. Since that time there has been a pronounced alteration in the outlook of such diseases as diabetes, pernicious anemia and nephritis, to mention only a few of the outstanding conditions that can be modified favorably by appropriate treatment. Necessarily, this has called for a revision of certain sections of the book. Except for these comparatively few changes there has been no radical alteration in the context of the book. It gives a complete summary of every conceivable type of condition which might cause death, arranged in alphabetical order. A minor criticism might be that there is a disproportionate amount of space given to some of the conditions, chlorosis, for example, being given somewhat over two and a half pages, whereas coronary thrombosis has about one page assigned to it. All in all, with the exception of a few trivial criticisms, the book can be highly praised. It represents well balanced, conservative statements by well qualified authors as to the future outlook of practically every disease to which man is heir.

**The Heart Rate** By Ernst P. Boas, M.D., Associate Physician, Mount Sinai Hospital, New York, and Ernst F. Goldschmidt, Ph.D., Research Fellow (1930-1931), Department of Surgery, Yale University School of Medicine  
 Price, \$3.50 Pp 166, with 68 figures and 30 tables Springfield, Ill. Charles C. Thomas, 1932

The present volume records a study of the heart rates of fifty-one normal men and fifty-two normal women by means of the cardiograph, a device which permits, within certain practical limits, a continuous record of the heart rate over twenty-four or more hours. With this instrument the heart rate was studied during waking and sleeping states. The data were correlated with certain body measurements. Furthermore, the cardiac rate was studied during certain daily activities. In chapters VII and VIII one finds studies on the pulse rate made during various types of anesthesia and in certain disease conditions (cardiac insufficiency, valvular disease, myocarditis, exophthalmic goiter, neurogenic sinus, tachycardia, auricular fibrillations and complete heart block). Chapter I contains a delightful historical account of the knowledge of the pulse rate from antiquity to the present time. The book is well written, and affords valuable data on the subject offered.

**Elektrokardiographie für die ärztliche Praxis** By Prof. Dr. Erich Boden  
 Price, 12 marks Pp 160 Dresden Theodor Steinkopff, 1932

The disturbances of cardiac mechanism are a bugaboo to many physicians, and at the sight of a complicated looking electrocardiogram they frankly throw up their hands in despair. This state of affairs is not unintelligible, since simple and lucid expositions of the subject are difficult to find. Sir Thomas Lewis' "Mecha-

nism and Graphic Registration of the Heart Beat" still remains the great storehouse of information, but neither it nor the other smaller treatise on clinical electrocardiography seems to be widely read in this country

This little book by Boden—if the American reader is not scared off by a foreign language—is an admirable elementary exposition of electrocardiography "for the actual practitioner" Outstanding features are the exquisite tracings and diagrams, which really make the understanding of the usual terrors such as "flutter," "ventricular tachycardia" and "nodal rhythm" simple, even for the most timorous The author holds to conventional views, which might here and there be challenged by the special student, but perhaps in a work of this sort controversy had better be avoided

**Textbook of Medicine** Edited by J J Conybeare, M C, M D (Oxon), F R C P Second edition Price, \$7 Pp 1,004 New York William Wood & Company, 1932

The general character of the book is the same as in the previous edition, there being sections on dermatology, pediatrics, tropical medicine, diseases of the nervous system and general medicine Practically one fourth of the space is given over to the nervous system There are four additional contributors, making a total of fourteen, but the editor contributes by and large the greater portion of the material No orderly manner is followed in dividing the book into sections or divisions for the various authors More space is devoted to physiology and laboratory procedure than is done in books of the same scope by American authors

When it is realized how great a field the book attempts to cover, it is evident that the subject matter must be very limited and in many instances must reach the proportions of an outline Possibly it may have a place in the library of the general practitioner, but it can meet with little favor as a textbook

**Die Praxis der Grundsatzbestimmungen** By Viktor Niederwieser Price, 420 marks Pp 61 Berlin Julius Springer, 1932

This booklet presents the results of determinations of the basal metabolic rate made by the author on hundreds of patients, in different age groups and under varied conditions, together with copious citations from the literature The main points of interest are the rates obtained following the administration of medications, physical therapy and therapy with various rays, as well as sunlight, and those obtained during acute and chronic infections, disturbances of the internal secretions, pregnancy, tumors and a few psychoses

Unfortunately, many of the findings are either contradictory or inconclusive, with perhaps the exception of those obtained during the exposure to sunlight or ultraviolet rays and others made on patients with hyperactivity or hypo-activity of the ductless glands The material is well arranged and well presented, and the brochure as a whole is quite readable and instructive

**An Index of Treatment** By Various Writers Edited by Robert Hutchinson, M D, F R C P Tenth edition, revised Price, \$12 Pp 1,027 New York William Wood & Company, 1931

Belittle, if you will, an attempt adequately to cover the entire field of therapeutics in a single volume, but here is a nearly successful attempt In scope and quality, there is no comparable American text Its list of contributors reads like a section of a British "Who's Who in Medicine" Modestly promising only to provide the practitioner with a guide to treatment within moderate compass, one marvels at the completeness and amount of detail Eschewing fads and recommending conservative but also eclectic methods, each author attempts to give what he thinks is the most logical treatment of the disease he is considering Perhaps more noteworthy than the undoubted excellence of each contribution are the amount and variety of topics, which range from ingrowing toe-nails to hypnotism, from corns and bunions to dysparemia, from gunshot wounds to Dhobie's itch, from transfusions to electrotherapeutics

**Physical Chemistry for Students of Biology and Medicine** By David I Hitchcock Cloth Price, \$2.75 Pp 182 Springfield, Ill Charles C Thomas, 1932

Dr Hitchcock presents discussions of many of the fascinating aspects of physical chemistry which have come to have direct applications to medical and biologic problems membrane equilibria, enzyme action, equilibria in blood, the colloidal state, etc. While the handling of the subject is in a sense elementary and hence an old story to the expert, the criticism may be made that the reasoning is not developed in enough detail to make matters clear to the average physician or medical student. Over and over again one comes face to face, unexpectedly, with quite complicated mathematical formulas, evidently of obvious simplicity to the writer, but difficult for the reviewer. Perhaps some one can be persuaded to write as a prelude to this book another one in which the necessary mathematics is developed.

**Polyposis Gastro-Intestinalis** By Hans Tønnesen Pp 224 Copenhagen Arnold Busck, 1931

Based on a collection of Danish cases, the author gives a systematic discussion of gastro-intestinal polyposis. The material is handled in a thorough, yet simple manner, and while nothing fundamentally new is brought out, the monograph covers existing knowledge of the subject in an adequate way. The illustrations are excellent. The text is in German.

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### CORRECTION

In the article by Drs Robert C Moehlig and Gaylord S Bates, entitled, "Influence of the Pituitary Gland on Erythrocyte Formation," in the February issue of the ARCHIVES (51 207, 1933), the third line on page 221 should read "13 Nerve end corpuscles," and "2 cm" in the seventh line on page 227 should read "2 mm."

## HYDROPHOBIA

REPORT OF TWO FATAL CASES WITH PATHOLOGIC STUDIES IN ONE

DAVID RIESMAN, M D

W W FOX, M D

B J ALPERS, M D

AND

DAVID A COOPER, M D

PHILADELPHIA

In recent years rabies in man has become a rare disease, owing to the improved methods of prophylactic treatment and to laws requiring the registration of all dogs and the quarantining of any suspicious animals. We have observed two cases, one of which developed in spite of the accepted prophylactic treatment. The other was that of a woman, aged 22, who was admitted to the Philadelphia General Hospital on April 5, 1931. The report of this case must of necessity be incomplete, because the patient was in the hospital only eighteen hours and was so desperately ill and so agitated that all efforts had to be centered on treatment. Furthermore, the family refused to permit an autopsy, and the coroner on whom the responsibility ultimately fell did not investigate the case. The history that we obtained is a digest of information received from the patient herself on admission, from her brother, her mother and the hospital in which she was first treated. Where there was disagreement, an attempt has been made to follow what in our judgment seemed the most reliable authority.

### REPORT OF CASES

CASE 1—Mrs C P, a housewife, aged 22, was admitted to the Philadelphia General Hospital on April 5, 1931. The family history was negative, as was her past medical history. She was married at the age of 18, and had two children. She believed herself about two months pregnant. Her husband was living and well, but their married life had been stormy. He drank heavily, and on occasions her brothers had to protect her from his violence.

About two months before admission, on February 5, the patient was bitten by a dog. This dog, which had just been given to her husband as a pet, also bit him, and at least two or three other persons in the neighborhood. Because of this her husband returned it to the original owner, and it was subsequently killed in a dog fight. Mrs P was taken to a nearby hospital, where the wounds were described

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Read at the meeting of the College of Physicians, Section on Medicine, Philadelphia, April 27, 1931.

as "four small puncture wounds on the left wrist" They were treated with nitric acid, ammonia, iodine, alcohol and a dry dressing

On Friday, April 3 she complained of pain in her left arm and in her back. On the following day she felt worse. Her husband went out for medicine and did not return. She went to her mother's home, she was much agitated, and said that she was leaving her husband. She complained of tightness in her chest, and declared that she could not swallow anything. She was taken to a hospital where



Fig 1—A section through the midbrain showing the vessels infiltrated, especially in the colliculi, periaqueductal region and reticular substance, toluidin blue stain

she was told that she was all right. After she returned home, a doctor was called, who tried to give her some medicine. She choked on it, insisted that she could not swallow, and began to have "fits," characterized by screaming, gripping her chest and crying out that she could not breathe, and that air from an open door or window choked her. Her brother then took her to two other hospitals, at each of which a hypodermic injection of some sort was administered. Finally, two days

after the onset of symptoms, she was sent to the Philadelphia General Hospital. When first seen she was sitting up in bed and looking around apprehensively. She complained of a tight feeling in her chest, inability to swallow and difficulty in breathing. An open door or window made a draught that choked her. She

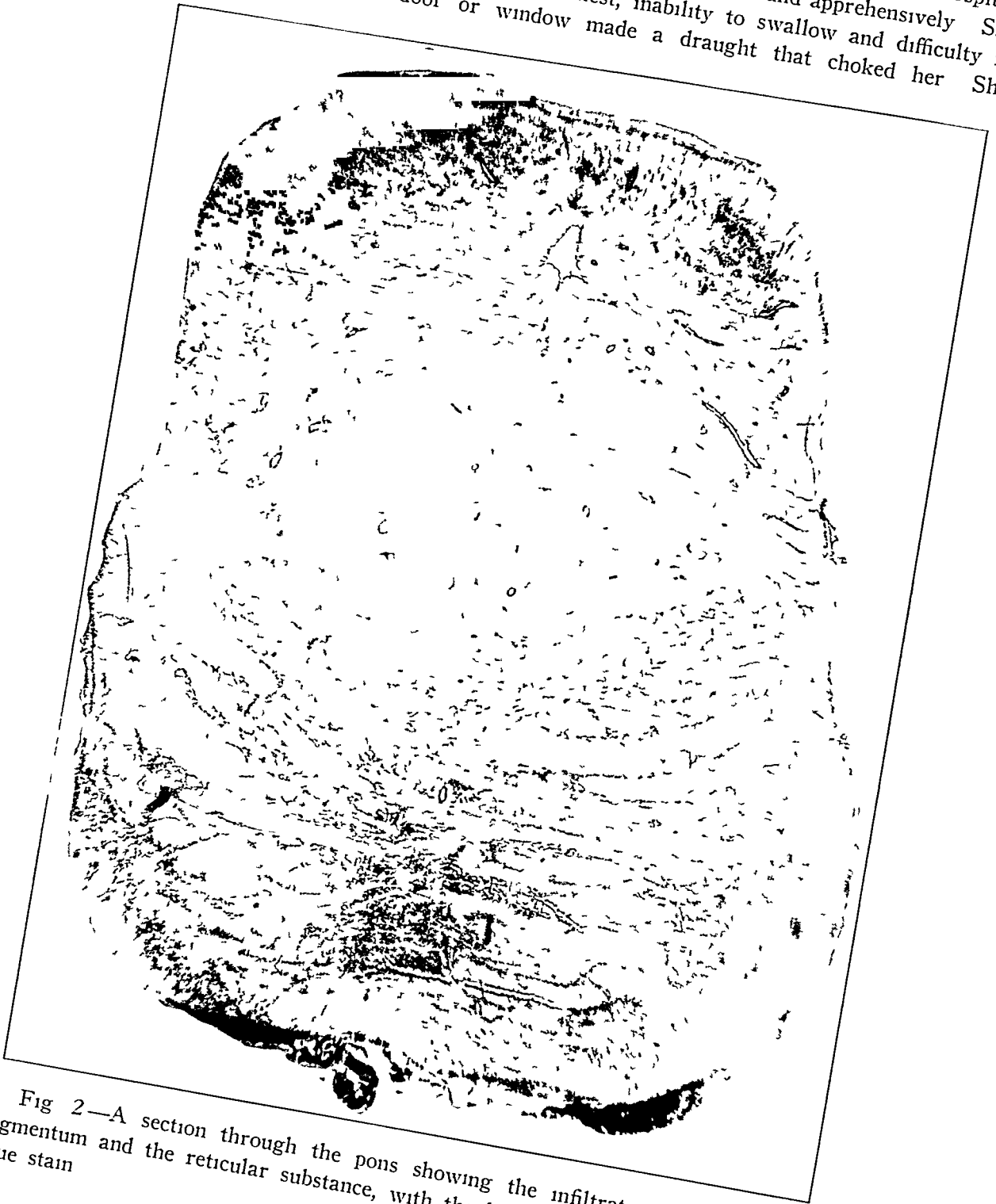


Fig 2—A section through the pons showing the infiltration, chiefly in the tegmentum and the reticular substance, with the basis pontis untouched, toluidin blue stain

objected to examination, insisting that each touch "choked" her. A fairly complete physical examination was achieved, however, during the course of the day. The findings were negative, except for widely dilated pupils which failed to react

to light or in accommodation, and a scanty, thin, white vaginal discharge. Her color was good, and despite her claims of difficult respiration, breathing was not noisy, and there was no cyanosis. The axillary temperature was 101.8 F, and the pulse rate, 120. During the morning she refused all medicines and complained that a proctoclysis choked her, she occasionally grasped the top of the bed and screamed loudly. The nurse was eventually able to soothe her, and even persuaded her to leave the door of her room ajar. She apparently drank water placed beside her when no one was looking. At noon she drank a cup of orange juice and ate



Fig 3—A section through the medulla showing the exudate, chiefly in the floor of the fourth ventricle and the reticular substance. Most of the exudate lies above the inferior olives, toluidin blue stain.

small helpings of chicken, potatoes and rice pudding, but refused water. There was no excessive salivation.

In the afternoon she became more and more excited. She was worried if the door of her room was allowed to be open. When it was closed, she complained that there was a nurse just outside the door. She insisted that the windows were open when they were not. Eventually, she began to curse and spit at every one, to scream loudly and to void involuntarily. The pulse became rapid, the color

became slightly bluish. She was put in restraint and  $\frac{1}{4}$  grain (0.016 Gm) of morphine sulphate and  $\frac{1}{150}$  grain (0.0003 Gm) of hyosine hydrobromide were given, after which she was transferred to the psychopathic department. In the evening she began to vomit a brown liquid. She also spat frothy white saliva, and the nurses reported that she was frothing at the mouth. She no longer screamed but lay talking and muttering to herself. At 10 p. m. the pulse became imperceptible, the color, pale and bluish, the axillary temperature was 103 F. At 11 p. m. the temperature was 106.4, and at 11.30 she died.

The diagnosis must obviously remain uncertain, although the case is entered on the hospital records as one of hydrophobia. So far, none of the other persons bitten by the dog has had any unfavorable symptoms. Since the patient's death, however, antirabic treatment has been instituted on all except her husband, who refused it.

CASE 2—The second case was that of a boy, aged 14 years, who was admitted to the University Hospital on Nov. 5, 1930, with fever, nervousness and instability



Fig. 4—A section through the cervical cord showing the inflammation almost entirely in the gray matter, toluidin blue stain

and salivation. He had been bitten by a stray dog on Oct. 11, 1930, twenty-five days prior to admission. The animal had a bloody mouth, as though it had been injured, and the boy was trying to aid it when he was bitten. The dog had disappeared and could not be located. The bite, which involved the left ear and cheek, was treated immediately in the Atlantic City Hospital, the wound being cauterized with phenol. Two days after the injury, the Pasteur prophylactic treatment was instituted, and a full course of treatment was given, which was completed a few days prior to admission. There were no untoward reactions. The local wounds had healed completely during that time. Throughout the week prior to admission the child had been more irritable than usual, and three days before he had complained of headache and had a coated tongue. He received a laxative, which he vomited. The next day he had a temperature of 101 F., and the headache was worse. He also complained of numbness and tingling in his left cheek and ear. These symptoms increased rapidly, and in addition, internal strabismus, diplopia and visual hallucinations appeared. The boy was restless and sleepless, and had difficulty in swallowing.

The past medical, family and social history was irrelevant.



When the boy was seen by one of us (D R), the most striking features were an intense restlessness, a flushed face and a continued flow of water from the mouth. The mouth seemed to be filled with saliva. Though the patient was conscious and could answer questions he seemed to have visual hallucinations with respect to surrounding objects. The temperature was 101 F, the pulse rate, 120. The lungs showed many coarse râles. The skin over the trunk and extremities was markedly hyperesthetic, but there were no paralyses of the limbs and no spasticity. The knee jerk was exaggerated. The right eye showed an internal strabismus, the pupils were dilated. Examination of the blood revealed hemoglobin, 90 per cent, red blood cells, 4,750,000, white blood cells, 26,200, of which 80 per cent were neutrophils, 10 per cent lymphocytes and 10 per cent monocytes.

Despite sedative treatment, the boy had several generalized convulsions. The temperature rose steadily to 107 F, and death occurred in a convulsion, six hours after admission.

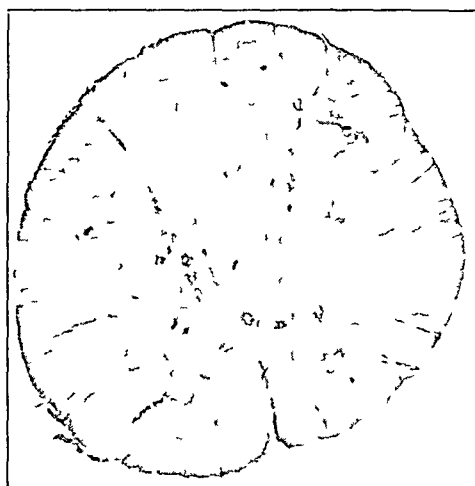


Fig. 5—The thoracic cord shows much less infiltration than the cervical cord.

The diagnosis was hydrophobia—acute encephalitis. The autopsy was performed shortly after death. The findings, except those in the brain and spinal cord, were insignificant.

*Gross Morbid Anatomy*—The brain and spinal cord showed little in the gross specimen. The brain was markedly edematous everywhere. It had a blue cyanotic appearance, owing to congestion of all the superficial vessels. The substantia nigra appeared somewhat depigmented. The spinal cord showed nothing of importance grossly, except a pinkish appearance of the gray matter, owing to the great prominence of the vessels. It, too, was swollen and edematous.

*Microscopic Changes*—In the gray substance of the base of the brain and in the gray matter of the spinal cord there was a marked inflammatory exudate, which was confined largely to the vessels, but which was spread diffusely throughout these tissues. The ganglion cells of the cortex showed marked changes.

The distribution of the lesions is a matter of great interest. The most pronounced reaction was found at the base of the brain. The cortex showed almost no evidence of inflammation, except for a mild meningeal exudate in a few places. Of the basal ganglia, the thalamus showed some active perivascular inflammatory foci. These were situated just under the ventricular ependyma. The other basal ganglia were relatively little involved. In the mesencephalon the inflammatory

reaction was most marked in the colliculi, around the aqueduct of Sylvius and in the reticular substance. The nucleus ruber was mildly infiltrated, and so, too, was the substantia nigra. The pes pedunculi showed some inflammatory foci. The greatest infiltration in the mesencephalon was in the periaqueductal gray matter, immediately around and below the iter. Infiltration tended to shade off gradually below this, though it was present everywhere in this section of the brain stem. The inflammatory reaction in the pons was practically confined to the tegmentum. The gray matter around the iter and fourth ventricle was markedly infiltrated with the reacting cells, but the basis pontis remained untouched. This was exceedingly striking. The entire tegmental gray matter was infiltrated and involved in

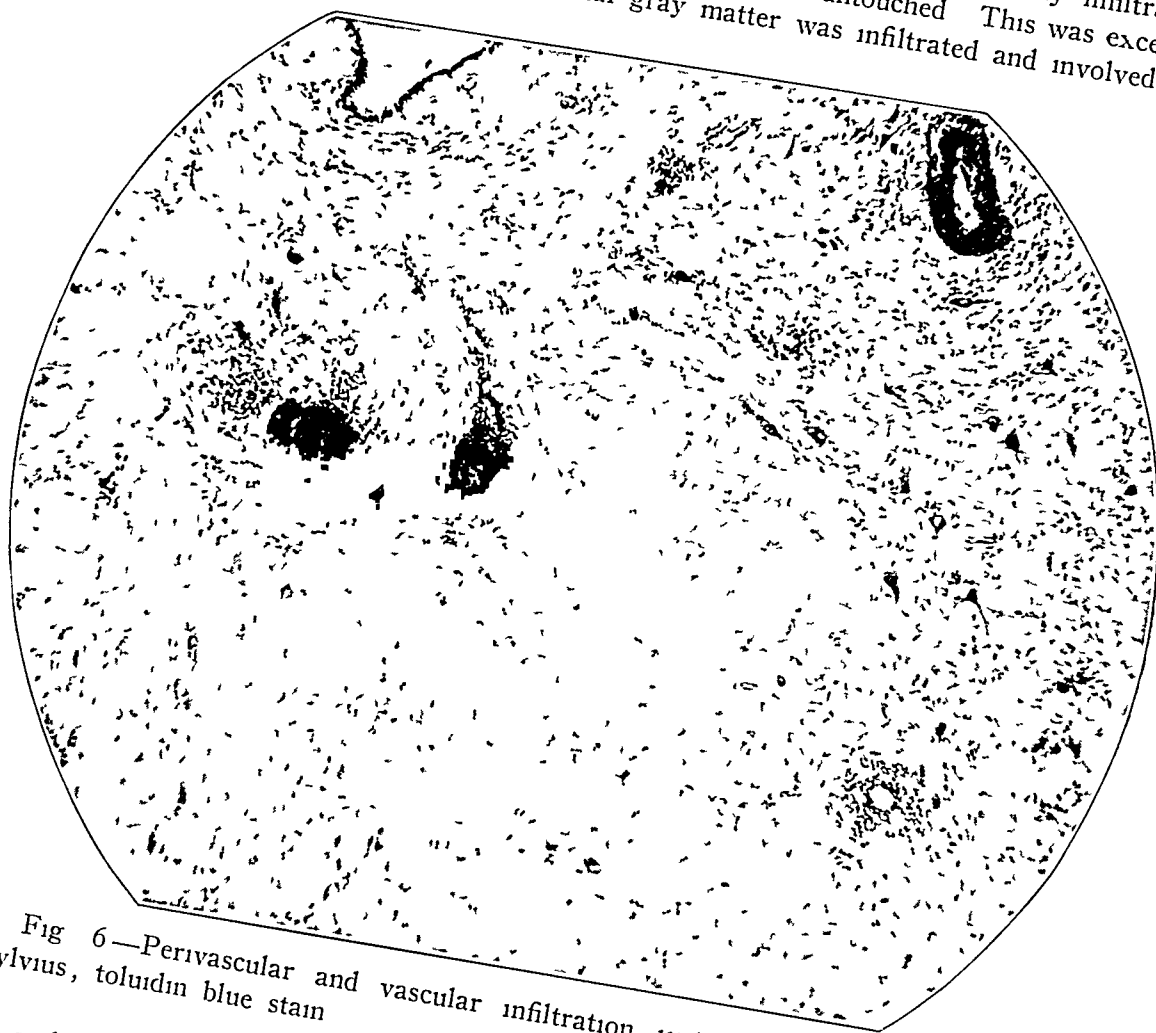


Fig 6—Perivascular and vascular infiltration just under the aqueduct of Sylvius, toluidin blue stain

the pathologic process. In the medulla the inflammation was found in the floor of the fourth ventricle and in the entire reticular substance. Here, too, the inflammation was confined practically entirely to the gray matter. It stopped at the level of the inferior olives. The latter were mildly infiltrated. As one descended from the medulla into the spinal cord, it was found that the gray matter was involved almost exclusively. The white substance was infiltrated mildly here and there, but practically all the changes were in the gray substance. The cervical and lumbar cords were severely involved, while the thoracic region was less severely attacked. Within the gray substance the anterior horns were more markedly affected than the posterior horns. It is thus evident that the process was confined almost entirely to the gray matter of the base of the brain and the spinal cord.

The nature of the exudate is of as much interest as its distribution. In the areas where the exudate was most pronounced, there was marked perivascular infiltration. This involved the adventitial sheaths of the blood vessels as well as the perivascular spaces. In some vessels the amount of exudate was tremendous, in others it was less pronounced. In some vessels the exudate was composed exclusively of lymphocytes, in others it consisted of lymphocytes and large mononuclear elements. Plasma cells were rarely seen. Around the vessels, within the tissue substance, were large groups of cells of noninflammatory nature. They were composed of large oval, round or crescentic vacuolated nuclei and an abundant

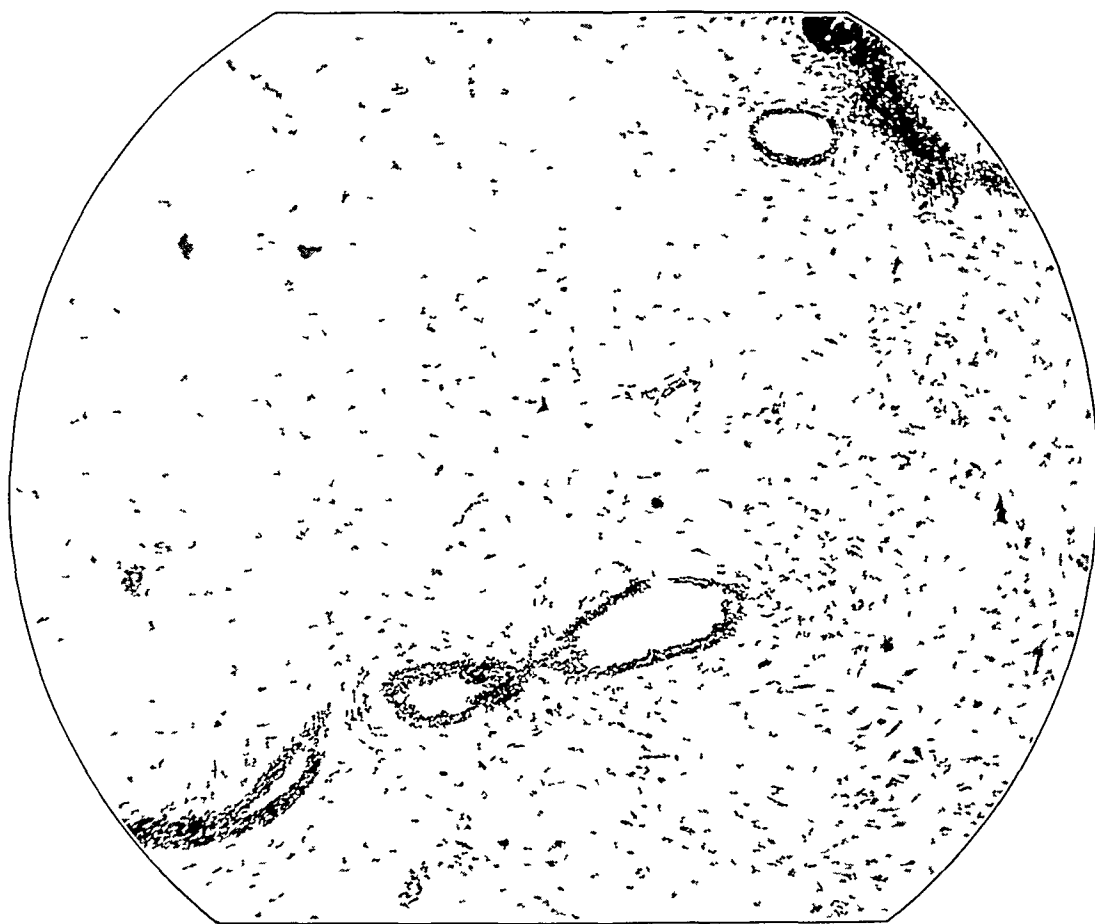


Fig 7—Inflammation in the floor of the fourth ventricle, toluidin blue stain

cytoplasm. They probably represented astrocytes among which were some fibroblastic elements. In some areas these cells constituted the major portion of the cellular reaction. They were spread throughout the involved areas, sometimes around vessels, but most often as a diffuse reaction within the tissue substance itself. They were particularly abundant in the spinal cord.

The meninges over the cortex, base of the brain and cord were mildly infiltrated here and there with lymphocytes. This meningeal infiltrate was, however, nowhere pronounced.

The cells of the cortex were almost universally degenerated. So, too, were the ganglion cells in the inflammatory areas and in the spinal cord. In the latter, the ganglion cells were virtually gone, but at a few levels groups of relatively intact

ganglion cells could be found. The cells in the cortex were swollen, their processes tortuous and enlarged, the nucleus homogeneous, the nuclear membrane absent, giving a poor differentiation between nucleus and cytoplasm, the nucleolus vacuolated and the cytoplasm without Nissl bodies. This sort of ganglion cell change was found in all the cortical layers and in all areas of the brain. There was no glial hyperplasia in the cortex.

The oligodendroglia was acutely swollen in the spinal cord. The astrocytes showed no changes in either the brain or the cord. Neurofibrillar stains showed an absence of neurofibrils within the anterior horn cells of the spinal cord.

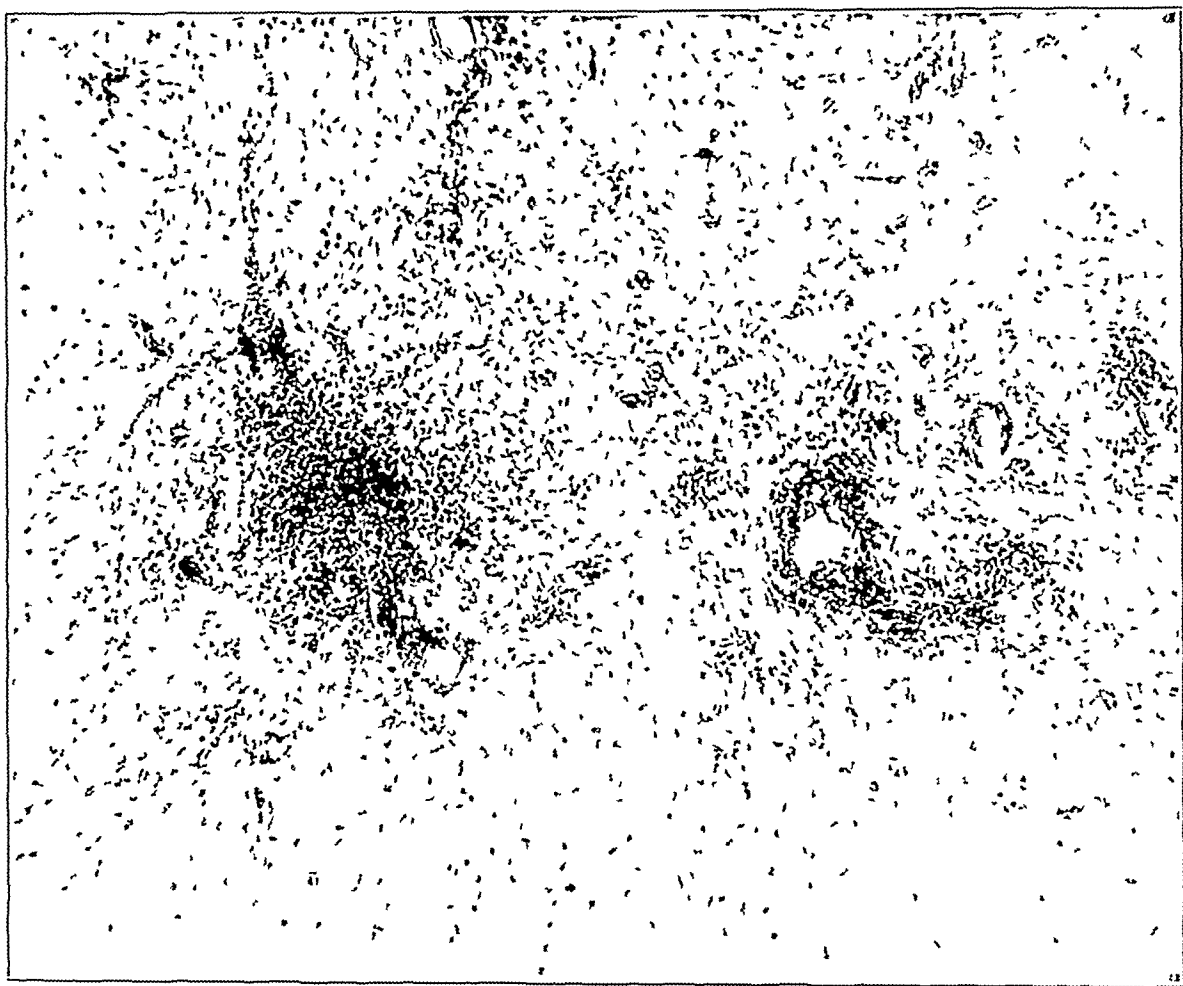


Fig 8—Marked infiltration with lymphocytes and neuroglia in the anterior horn of the cervical cord. Note the paucity of ganglion cells, toluidin blue stain.

An extremely careful search for Negri bodies failed to reveal these inclusions in the ganglion cells of the brain or spinal cord. However, four rabbits into which intracranial injections of an emulsion of the brain tissue had been made died on the tenth, eleventh, eleventh and fifteenth days respectively, the symptoms being those of rabies; at autopsy, typical Negri bodies were found, thus confirming the diagnosis of rabies.

#### PATHOLOGY OF RABIES

The pathologic changes in the nervous system in rabies are characterized by the presence of both inflammatory and degenerative

products Schaffer first called attention to these two processes in cases of lyssa. The inflammatory changes are characterized by a lymphocytic infiltration of the vascular adventitia in the early stages of the disease, followed by a filling of the perivascular lymph spaces with inflammatory cells, and eventual infiltration of the parenchyma. Lymphocytes constitute the majority of the exudative cells, plasma cells are less abundant, polymorphonuclear cells are rarely seen. The inflammation is accompanied by proliferative changes on the part of the neuroglia of both a diffuse and a focal nature. Babes described glial foci which he considered characteristic of rabies, but his descriptions have not been widely accepted. Achucarro has observed proliferative changes in the neuroglia, especially in the cornu ammonis. In addition, he found typical rod cells containing fat droplets in the cornu. Collado described hypertrophy of microglia cells in rabies. This has also been found by Loewenbeig. In our own case, the glial reaction was intense throughout the entire involved area, varying in intensity apparently in direct proportion to the severity of the inflammation. Most of the neuroglial cells are astrocytes. In our case the oligodendroglia, especially in the spinal cord, reacted by an acute swelling. The microglia took no part in the process.

The degenerative changes found in the nerve cells of the cortex and elsewhere are not as a rule in proportion to the degree of the inflammatory changes. There may be pronounced evidences of inflammation and only mild degenerative changes in the nerve cells of the brain. The reverse is also found—the degeneration of the cells may be pronounced and universal and inflammatory evidences only slight. Klarfeld believes that there are two separate and distinct processes in rabies: inflammatory and degenerative. These have apparently no clear relationship to each other. In one of his patients he found inflammatory changes limited to the pons and medulla and degenerative changes in the cerebrum and cerebellum. In another patient there were Babes' nodules and inflammation in the spinal cord, with no inflammation but active degeneration in the cerebrum and cerebellum. Spatz believes that the independent degenerative changes in the nerve cells may play an active rôle in the disease. The degeneration in the ganglion cells of the cortex is manifested by poor staining of the cell body, a loss of Nissl bodies, the formation of small bodies of chromatin in the nucleus, vacuolization, fatty degeneration, sclerosis and pigment atrophy. In our case the ganglion cells were swollen, the processes unduly visible, swollen and tortuous, the cytoplasm without Nissl bodies or with pulverized remains of these, the nucleus homogeneous and pale, the nucleolus often vacuolated and the cells containing fat. Cajal has described a simplification of the fibrillar network in the ganglion cells in rabies.

with some thickening of the neurofibrils, especially at the edge of the cells. This has been confirmed by Achucarro, who found these changes in the spinal ganglion cells. The change occurs late in the disease.

The independence of the inflammatory and degenerative processes is well illustrated in our case, in which there was marked inflammation at the base of the brain and in the spinal cord, and universal ganglion cell degeneration in the cortex, with practically no evidence of inflammation in this part of the brain. The independence of the two processes must not be overemphasized, however, because there were pronounced degenerative changes in the ganglion cells within the infiltrated areas of the brain. In the cortex, however, degeneration was pronounced, without the inflammation which was so marked at the base of the brain. There may, therefore, be two processes going on at the same time: inflammatory at the base of the brain and degenerative in the cortex. The degree of intensity of the degenerative process is not dependent in any way, apparently, on the inflammatory change. This point is well illustrated in two cases reported by Schukri and Spatz. In one case, there were inflammatory changes of a pronounced degree at the base of the brain, with only mild degenerative changes in the ganglion cells within the inflamed areas and practically no degeneration of the ganglion cells in the cortex. In their second case, there were likewise pronounced inflammatory changes at the base, with marked and universal degenerative changes in the nerve cells. The intensity of the inflammatory reaction was similar in the two cases, but the degeneration differed perceptibly in both.

Negri bodies are found in the dog's brain in rabies in the majority of instances. They have not been reported very often in man, though it seems to be accepted that they should be present as frequently in the human brain as in the dog's brain in hydrophobia. Viets reported a case in a human being with typical Negri body formation. A careful search in our case failed to reveal Negri bodies anywhere in the central nervous system. The two cases reported by Schukri and Spatz also showed no Negri bodies. Both of these cases, like ours, followed bites on the face, and were characterized by a very rapid clinical course. In the first case, which followed a wolf bite, death occurred twenty-nine days after the bite and in the second case, fifteen days after the bite. It is possible that the failure to find Negri bodies in the brains in cases of rabies may be related in some way to the acuteness of the disease. In both the cases of Schukri and Spatz and in our own case the course was extremely rapid, and it may be that Negri bodies had no time to form. Cases of rabies without the formation of Negri bodies have been reported by Maas, Abba and Borman, Leutz, J. Koch and Goldbeig. Koch reported four such cases.

## DISTRIBUTION OF LESIONS AND NATURE OF RABIES

Recent investigations, particularly those of Spatz, Schukin and Spatz, and Seifried and Spatz tend to classify rabies as an encephalitis and to group it with the encephalitides, which include epidemic encephalitis, poliomyelitis, Borna disease in horses, rabies, distemper and chicken plague.

Klarfeld first called attention to the similarity of the pathologic findings in lyssa and epidemic encephalitis. Later Schukin and Spatz studied two cases of rabies chiefly from the standpoint of the distribution of the lesions. They found marked involvement of the midbrain by the inflammatory process, particularly severe in the substantia nigra. The periaqueductal gray matter was rather severely involved, and the nucleus ruber was only mildly infiltrated. In the pons the inflammatory changes were most marked in the tegmentum—in the vicinity of the third and fourth ventricle. More anteriorly there were isolated areas of infiltration in the floor of the third ventricle, but none in the cortex. The distribution of the inflammation in these two cases, particularly the marked involvement of the midbrain and substantia nigra, in addition to the similarity in the nature of the exudate, led Schukin and Spatz to conclude that rabies and epidemic encephalitis were closely allied and should be placed together in the group of encephalitides. Hassin had previously shown that encephalitis and poliomyelitis are related, the only difference in the two diseases being that in epidemic encephalitis the pathologic changes tended to diminish spinalward, whereas in poliomyelitis they tended to diminish cerebralward. The intensity and distribution of changes in the two diseases may be so similar that they cannot be distinguished. The work of Schukin and Spatz has been confirmed in four cases of rabies by Loewenbeig, except that in two of his cases he found marked meningeal infiltrations. More recently, Seifried and Spatz have demonstrated that Borna disease, which is an encephalitis occurring in horses, is similar in all respects to rabies and the other encephalitides, including epidemic encephalitis, rabies, poliomyelitis and other diseases.

According to Seifried and Spatz, the characteristics which distinguish these various encephalitides are (1) absence of meningeal reaction, (2) predominant involvement of the gray matter, (3) a non-purulent type of infection, the reaction consisting of lymphocytes, plasma cells and large mononuclear elements, (4) a glial proliferation of a diffuse and focal nature, and (5) a lack of hemorrhages and softenings. Differences between the various members of the group are those of degree, a local meningitis is more common in poliomyelitis than in the other diseases and leukocytes play a more active rôle in poliomyelitis than in the other encephalitides.

The distribution of the pathologic changes and the inflammation is very much the same in epidemic encephalitis, poliomyelitis, rabies and Borna disease. The inflammatory exudate affects chiefly the gray matter at the base of the brain, involving particularly the colliculi, the periaqueductal gray matter, the substantia nigra and the tegmentum of the pons and medulla, especially the parts just under the fourth ventricle.

In the pons the basis escapes almost entirely. In the medulla the exudate is most active above the inferior olives. Spatz emphasizes the marked involvement of the substantia nigra in rabies, but in our case this nucleus was not particularly affected. In the hypothalamus the portions bordering on the ventricles are most involved. The tuber cinereum and infundibulum are special sites of election. In the fore-brain the basal ganglions are most involved by the exudate, especially the caudate nucleus and parts of the thalamus. The changes in the cortex are mild.

In our case the involvement of the spinal cord was pronounced, more even than in poliomyelitis. While the various diseases which are grouped in this class of encephalitides show some differences in distribution, they tend to have characteristics in common which would seem to justify the classification proposed.

From a clinical standpoint the cases here reported bring out several important features: first, the necessity of thoroughly cauterizing the wound, preferably with fuming nitric acid instead of with phenol or other caustic substances. Animal experiments have shown that wounds promptly and thoroughly cauterized with nitric acid are seldom followed by rabies.<sup>1</sup>

The incubation period in the second case was about three weeks, which is considerably below the average of forty days. The shortest incubation period on record is twelve days, the longest, two years. The incubation period tends to be shorter in children than in adults and in cases in which the bite is about the head and face. Both of these factors bear on our case. Recently it has been recommended that more active treatment be given to patients who had bites about the face and head, so as to produce immunity more rapidly. Generally it is considered that at least fourteen days must elapse after completion of the treatment with vaccine before immunity is attained. Therefore, in any case in which the offending dog cannot be traced, thorough cauterization of the wound with fuming nitric acid should be done and antirabic treatment begun at once. If the wound is on the face, the routine treatment should be intensified. The danger of paralysis due to treatment is practically negligible, and of those in whom it develops, about 85 per cent make a complete recovery.

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<sup>1</sup> In the first case thorough cauterization did not protect the patient from the disease.



# TREATMENT OF SECONDARY ANEMIA

WITH SPECIAL REFERENCE TO THE USE OF LIVER EXTRACT  
INTRAMUSCULARLY

WILLIAM P MURPHY, M D

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The comparative value of whole liver, ferrous carbonate, liver extract (fraction G of Cohn) and various combinations of these substances in the treatment of secondary anemia of man was discussed in three previous communications<sup>1</sup> The present report is concerned with observations as to the relative merit of ferric ammonium citrate, ferric citrate, liver extract for use in secondary anemia (Whipple<sup>2</sup>), solution of liver extract for intramuscular injection<sup>3</sup> and a comparison of these with the substances previously reported on for the treatment of the same type of anemia

## METHODS OF STUDY

Since the methods used in the study of the cases reported here have been similar in most respects to those described previously,<sup>4</sup> a complete description of them will not be repeated Hemoglobin determinations have been made by means of the Osgood-Haskins<sup>5</sup> modification of the Sahli method By this method 100 per cent is equivalent to 13.8 Gm of hemoglobin per hundred cubic centimeters of blood This may be considered a low normal level for women Determinations of the whole

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From the Medical Clinic of the Peter Bent Brigham Hospital

This study was aided by a grant from the De Lamar Mobile Fund of the Harvard Medical School

1 (a) Murphy, W P, and Powers, J H The Value of Liver in the Treatment of Anemia Due to Hemorrhage, *Surg, Gynec & Obst* **48** 480 (April) 1929 (b) Murphy, W P Observations on the Treatment of Anemia, *ibid* **50** 246 (Jan) 1930 (c) Powers, J H, and Murphy, W P The Treatment of Secondary Anemia, *J A M A* **96** 504 (Feb 14) 1931

2 Whipple, G H, Robschert-Robbins, F S, and Walden, G B Blood Regeneration in Severe Anemia XXI A Fraction Potent in Anemia Due to Hemorrhage, *Am J M Sc* **179** 628 (May) 1930

3 Murphy, W P The Parenteral Use of Liver Extract in Pernicious Anemia, *J A M A* **98** 1051 (March 26) 1932 This solution was prepared by Lederle Laboratories of New York

4 Footnote 1a and c

5 Osgood, E E, and Haskins, H D A New Permanent Standard for Estimation of Hemoglobin by the Acid Hematin Method, *J Biol Chem* **57** 107 (Aug) 1923

blood iron,<sup>6</sup> have been continued in these cases as an aid in following the changes in the blood. For reasons which will be discussed in a subsequent paper, the procedure of Wong<sup>7</sup> for the determination of whole blood iron has been used instead of that of Kennedy<sup>8</sup>. By this method the lower limit of normal for women is considered as approximately 43 mg per hundred cubic centimeters of blood, which is about 6 mg higher than that previously reported.<sup>9</sup> In order to calculate the hemoglobin from the figure for whole blood iron, each milligram of iron may be considered equal to 0.305 Gm of hemoglobin. The reticulocytes were counted during the first few days of treatment in several cases, but as the majority of the patients were treated outside of the hospital it was not possible in all. Since the reticulocyte curves are of little value in analyzing the results of treatment of the patients, they will not be shown.

The blood of each patient was examined at weekly intervals when possible, but in the interest of brevity a complete record of the observations is not shown in the tables. Although the final figures may not indicate in each instance an entirely normal state of the blood, an effort has been made to utilize the data for purposes of comparison only to the point at which definite improvement was interrupted for one reason or another. Therefore, in order to compare the results observed in the several groups, it is necessary to take into consideration not only the number of days during which treatment was given but also the level of the hemoglobin and red blood cell counts at the time treatment was begun and the levels to which they improved.

In order to make the record of the effect of the treatment used comparable to that recorded in previous communications, the iron salt was given in some instances in such an amount daily that it would again be the "minimal" effective dose<sup>10</sup> and the actual iron content of the dose used essentially the same as that used previously. Both ferric ammonium citrate and ferric citrate contain about twice as much iron per unit of weight of the salt as is present in pills of ferrous carbonate, U. S. P. That is, a dose of 1 Gm of ferric ammonium citrate contains

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6 Murphy, W. P., Lynch, R., and Howard, I. M. The Value of Determinations of the Iron Content of Whole Blood, *Arch. Int. Med.* **47**: 883 (June) 1931. Footnote 1c.

7 Wong, S. Y. Colorimetric Determination of Iron and Hemoglobin in Blood, *J. Biol. Chem.* **77**: 409 (May) 1928.

8 Kennedy, R. P. The Quantitative Determination of Iron in Tissues, *J. Biol. Chem.* **74**: 385 (Aug.) 1927.

9 Footnote 1c.

10 A dose which may reasonably be expected to produce improvement of the blood but which probably does not produce the best results in the majority of patients.

approximately 170 mg of iron, and of ferric citrate, 186 mg, whereas an essentially comparable amount of iron (173 mg) is present in pills of ferrous carbonate given in a dosage of 1.8 Gm

#### COMMENT ON TABLES AND CASES

The results obtained by each form of treatment are tabulated separately in order to make a comparison of results more satisfactory

The anemia present in the majority of the patients primarily considered in this paper may be classified as of the chronic chlorotic type or idiopathic hypochromic anemia in which there is a low hemoglobin level with relatively little alteration in the red blood cell count. In a few instances, nutritional factors and chronic loss of blood probably played a rôle in the production of the anemia. Those patients treated with ferrous carbonate referred to in previous papers<sup>4</sup> were, in most instances, anemic owing to chronic hemorrhage. No distinction has been made between the effect of treatment on anemia from the various causes, although those anemic from hemorrhage probably respond to treatment somewhat more readily than do those anemic from other causes.

Observations made during the course of treatment of twelve patients with ferric ammonium citrate and intramuscular injections of solution of liver extract are recorded in tables 1 and 1 *A*. Intramuscular injections only were given to five of these patients for a period before the iron salt was administered and to one other who did not receive iron. The results obtained in these six patients are shown in table 1 *B*.

The amount of solution of liver extract given to each patient varied considerably as shown in tables 1 and 1 *B*. The initial injection was usually the amount of solution derived from 100 to 200 Gm of liver, and in some instances this dose was repeated within twenty-four hours. Thereafter at intervals varying from one to three weeks during the period of observation, an injection of 3 or 5 cc prepared from 100 Gm of liver was given. When iron was used it was given either in solution or capsule<sup>11</sup> in daily doses of 3 Gm of the salt except in three instances (cases 1, 2 and 5) in which 6 Gm was used. In case 1 the dose was reduced to 3 Gm daily after the first three weeks. The solution of liver extract (Lederle) used intramuscularly is iron-free.

The intramuscular injections alone usually resulted in some increase in the red blood cell count with little change in the hemoglobin level. In three instances (cases 7, 11 and X), the hemoglobin increased slightly. A very restricted diet was, no doubt, a contributing factor to the anemia observed in the first of these patients. During the period of observation in which he received only the injections, he received a diet high in iron

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11 Prepared by the Lederle Laboratories, New York

TABLE 1—*Record of Patients Treated with Solution of Liver Extract Intramuscularly and Ferric Ammonium Citrate by Mouth*

Case	Red Blood Cells, Millions per C Mm		Hemoglobin, Gm per 100 Cc		Blood Iron, Mg per 100 Cc		Liver Solution Injections		Daily Dose of Iron Salt, Gm	Number of Days Treated
	Initial	Final	Initial	Final	Initial	Final	Date	Amount Injected and Liver from Which Derived		
1	4 49	5 27	7 31	11 87	25 70	44 20	12/12/31	{ 1 2 cc = 24 Gm 5 0 cc = 100 Gm 3 0 cc = 100 Gm }	6	25
							12/13/31			
	5 27	5 74	11 87	15 59	44 20	49 50	1/ 6/32			
							1/20/32	{ 3 0 cc = 100 Gm 1/27/32 { 3 0 cc = 100 Gm }	3	31
2	2 72	5 51	3 04	14 90	10 37	44 60	4/15/32	6 cc = 200 Gm	6	77
							4/18/32	6 cc = 200 Gm		
							4/20/32	3 cc = 100 Gm		
							4/27/32	3 cc = 100 Gm		
							5/ 4/32	3 cc = 100 Gm		
							5/18/32	3 cc = 100 Gm		
							6/ 1/32	3 cc = 100 Gm		
							6/15/32	3 cc = 100 Gm		
							6/28/32	3 cc = 100 Gm		
3	2 71	5 17	3 04	11 45	12 40	37 30	1/23/32	0 2 cc = 4 Gm	3	42
							1/24/32	5 0 cc = 100 Gm		
							1/25/32	5 0 cc = 100 Gm		
							1/29/32	5 0 cc = 100 Gm		
							2/19/32	3 0 cc = 100 Gm		
							2/26/32	3 0 cc = 100 Gm		
							3/ 4/32	3 0 cc = 100 Gm		
4*	4 86	6 05	7 73	13 39	29 40	42 70	3/ 2/32	6 cc = 200 Gm	3	21
							3/16/32	3 cc = 100 Gm		
							3/23/32	3 cc = 100 Gm		
5	5 19	5 65	8 97	14 90			4/21/32	3 cc = 100 Gm	6	63
							4/28/32	3 cc = 100 Gm		
							5/ 5/32	3 cc = 100 Gm		
							5/19/32	3 cc = 100 Gm		
							5/27/32	3 cc = 100 Gm		
6	4 72	5 38	8 42	11 73	29 20	37 70	5/17/32	6 cc = 200 Gm	3	35
							5/25/32	3 cc = 100 Gm		
							6/ 1/32	3 cc = 100 Gm		
							6/ 8/32	3 cc = 100 Gm		
							6/15/32	3 cc = 100 Gm		
							6/22/32	3 cc = 100 Gm		
7*	4 17	4 83	10 07	13 66	40 30	42 00	12/28/31	5 cc = 100 Gm	3	21
8	4 83	5 59	8 28	12 14			5/18/32	3 cc = 100 Gm	4	21
							5/21/32	6 cc = 200 Gm		
							5/27/32	3 cc = 100 Gm		
							6/ 6/32	3 cc = 100 Gm		
							6/13/32	3 cc = 100 Gm		
9*	3 91	4 88	4 55	12 76	18 00	41 80	5/24/32	3 cc = 100 Gm	3	63
							6/ 1/32	3 cc = 100 Gm		
							6/22/32	3 cc = 100 Gm		
							7/ 6/32	3 cc = 100 Gm		
							7/13/32	3 cc = 100 Gm		
							7/20/32	3 cc = 100 Gm		
10*	5 00	5 53	5 24	12 42	19 10	40 10	7/27/32	3 cc = 100 Gm	3	49
							6/15/32	3 cc = 100 Gm		
							6/29/32	3 cc = 100 Gm		
							7/ 6/32	3 cc = 100 Gm		
							7/13/32	3 cc = 100 Gm		
							7/27/32	3 cc = 100 Gm		
11*	6 14	6 25	10 21	13 11	35 70	41 15	8/ 3/32	3 cc = 100 Gm	3	35
							7/ 6/32	3 cc = 100 Gm		
							7/13/32	3 cc = 100 Gm		
							7/20/32	3 cc = 100 Gm		
							7/27/32	3 cc = 100 Gm		
							8/ 3/32	3 cc = 100 Gm		
12	2 67	5 16	4 97	11 73	18 05	39 20	6/23/32	6 cc = 200 Gm	1 8†	49
							6/29/32	3 cc = 100 Gm		
							7/ 6/32	3 cc = 100 Gm		
							7/13/32	3 cc = 100 Gm		
							7/20/32	3 cc = 100 Gm		
							7/27/32	3 cc = 100 Gm		
							8/ 3/32	3 cc = 100 Gm		

\* See table 1B for the results of treatment with solution of liver extract alone. The red blood cell count has been increased in cases 4, 7, 9 and 11 by the previous treatment.  
† Pills of ferrous carbonate, U S P

content (but without liver), which may in part account for the increase in hemoglobin. The third of the three patients entered the hospital with a generalized skin eruption of unexplained origin and an anemia. Following the injections, the red blood cell count increased, the eruption cleared up and the patient's general condition improved strikingly up to the time of discharge from the hospital. Further follow-up treatment was not possible.

Improvement in the patients treated with injections of solution of liver extract and iron by mouth has been unusually rapid (tables 1 and 1 A),<sup>11a</sup> and in the majority the final red blood cell count, hemo-

TABLE 1A—Detailed Record of Changes in the Hemoglobin in Patients

Case	Initial			Increase in Hemo											
	Red Blood Cells	Hemo globin	Blood Iron	7 Days	Per Day	14 Days	Per Day	21 Days	Per Day	28 Days	Per Day	35 Days	Per Day	42 Days	Per Day
1	4.49†	7.31	25.70			1.52	138.2	3.87	215.0	4.56	132.5	4.28	134.0	7.04	180.5
2	2.72	3.04	10.37	0.41	58.5	2.07	147.6	4.83	230.0			7.47	213.0		
3	2.71	3.04	12.40	1.10	157.0	3.17	226.2	3.86	184.3	7.17	256.0	7.59	216.8	8.14	200.2
4	4.86	7.73	29.40	2.48	354.2	4.00	286.0	5.66	269.5						
5	5.19	8.97								4.83	172.5				
6	4.72	8.42	29.20	0.41	58.5			2.90	138.2	4.00	142.9	3.31	94.6		
7	4.17	10.07		1.25	178.5	1.80	128.4	3.59	171.0						
8	4.83	8.28				1.66	118.5	3.86	184.3						
9	3.91	4.55	18.00	1.25	178.5	3.73	259.1	4.70	222.9	5.25	187.5	5.94	169.5	6.35	151.2
10	5.00	5.24	19.10			1.33	98.5	2.90	138.1	3.45	123.2			6.72	160.0
11	6.14	10.21	35.70	1.24	177.1	0.55	39.3			2.35†	83.9	2.90	82.8		
12	2.67	4.97	18.05	1.38	197.1	2.62	187.1	5.24	249.1	6.03	215.5	5.94	169.6	6.35	151.2
Averages				1.19	170.0	2.24	162.9	4.14	200.2	4.71	170.5	5.35	154.3	6.92	163.6

\* The gain in hemoglobin at intervals of seven days is shown in grams, the gain per day, in milligrams.

† The calculations were actually based on intervals three days shorter than listed.

‡ No iron was given for one week.

§ No iron was given for two weeks.

globin and whole blood iron levels have been higher than in the other groups reported. One patient (case 3) had a complicating mild arthritis with cholecystitis and cholelithiasis. Another patient (case 9) improved satisfactorily in spite of the fact that she took care, practically night and day, of four children very ill with whooping cough.

In tables 2 and 2 A are recorded observations obtained in following the effect on the blood of sixteen patients treated with ferric ammonium citrate. The first eight patients received 1 Gm of the salt daily, whereas the others received 2, 3 or 6 Gm daily.

11a Seven other patients have been treated by this method since the tables were prepared, so the results are not recorded therein. Improvement in these seven has been more striking than in the twelve cases the results of which are recorded in tables 1 and 1 A.

One patient of this group (case 17) had a basal metabolic rate of minus 18 per cent and for twenty-three days before beginning iron therapy received daily 0.130 Gm of thyroid substance. Although the basal metabolic rate had increased to minus 5 per cent and she felt better, there had been little change in the blood. Thyroid medication was continued along with the iron. Prior to starting iron treatment, another patient (case 19) received daily for forty-two days 120 Gm of "yellow" bone marrow preserved by freezing. During this period of treatment, the red blood cell count increased from 2,410,000 to 2,970,000 and the hemoglobin from 4.28 to 4.83 Gm per hundred cubic centi-

*Treated with Liver Solution and Ferric Ammonium Citrate as in Table 1*

globin *										Final			Total Gain		
49 Days	Per Day	56 Days	Per Day	63 Days	Per Day	70 Days	Per Day	77 Days	Per Day	Red Blood Cells	Hemo globin	Blood Iron	Red Blood Cells	Hemo globin	Blood Iron
7.73	172.0	8.28	156.4							5.74	15.59	49.50	1.25	8.28	23
9.79	199.0			10.48	166.3			11.86	154.0	5.51	14.90	44.60	2.79	11.86	34
										5.17	11.45	37.30	2.46	8.14	24
										6.05	13.39	42.70	1.19	5.66	13
				5.93	94.2					5.65	14.90		0.46	5.93	
										5.38	11.73	37.70	0.66	3.31	8
										4.83	13.66	42.00	0.66	3.59	
										5.59	12.14		0.76	3.86	
6.638	135.4	6.82	121.8	8.21	130.3					4.88	12.76	41.80	0.97	8.21	23
7.18	146.5									5.53	12.42	40.10	0.53	7.18	21
										6.25	13.11	41.15	0.11	2.90	5.4
6.76	138.0									5.16	11.73	39.20	2.49	6.76	21.1
7.62	155.5	7.55	134.8	8.21	130.4			11.86	154.0					6.32	19

eters of blood. In a similar period of time, with 1 Gm of ferric ammonium citrate the red blood cell count rose from 2,970,000 to 4,150,000 and the hemoglobin level from 4.83 to 8.69 Gm per hundred cubic centimeters of blood. Subsequent improvement in this patient did not occur as rapidly as in most of the others, no doubt partly because of her inability to secure proper food after her discharge from the hospital. The same factor probably was an important contributing cause of the anemia. The anti-anemia diet which she received for seventy days in the hospital may have aided in her improvement. The patient in case 20 was given for thirty-seven days six teaspoonfuls daily of a colloidal iron compound. No definite change in the blood occurred, whereas with 1 Gm of ferric ammonium citrate given daily for thirty-five days the red blood cell count rose from 4,290,000 to 4,960,000 and the hemo-

globin from 5.24 to 8.28 Gm per hundred cubic centimeters of blood. One other patient received the same preparation without improvement but later failed to carry out treatment with another form of iron so the results are not recorded. Two patients (cases 24 and 25) received intravenous injections of colloidal iron hydroxide, averaging 3 cc daily (each 3 cc containing 4 mg of iron) before oral treatment was begun, and the figures showing the results of this treatment are recorded in tables 3 and 3A. One of these (case 24) was observed for seventy days during this form of treatment and in addition received several

TABLE 1B—*Record of Patients Treated with Solution of Liver Extract Intramuscularly without Iron*

Case	Red Blood Cells, Millions per Cc Mm		Hemoglobin, Gm per 100 Cc		Blood Iron, Mg per 100 Cc		Liver Solution Injections		Number of Days
	Initial	Final	Initial	Final	Initial	Final	Date	Amount Injected and Liver from Which Derived	
4	4.40	4.86	8.97	7.73	31.70	24.90	2/ 3/32 2/ 4/32	6 cc = 200 Gm 6 cc = 200 Gm	28
7	3.25	4.17	8.14	10.07	30.03	40.30	11/18/31 11/19/31 11/20/31 12/ 8/31 12/ 9/31	0.2 cc = 4 Gm 10.0 cc = 200 Gm 10.0 cc = 200 Gm 10.0 cc = 200 Gm 4.0 cc = 80 Gm	40
9	3.37	3.91	5.93	4.55	17.61	15.00	4/22/32 4/27/32 5/24/32	6.0 cc = 200 Gm 6.0 cc = 200 Gm 3.0 cc = 100 Gm	32
10	5.37	5.00	5.33	5.24	21.10	19.10	5/19/32 5/20/32 5/26/32 6/ 1/32 6/ 8/32 6/15/32	6 cc = 200 Gm 6 cc = 200 Gm 3 cc = 100 Gm 3 cc = 100 Gm 3 cc = 100 Gm 3 cc = 100 Gm	27
11	5.56	6.14	9.80	10.21	36.50	35.70	5/31/32 6/ 8/32 6/15/32 6/22/32 6/29/32 7/ 6/32	3 cc = 100 Gm 3 cc = 100 Gm 3 cc = 100 Gm 3 cc = 100 Gm 3 cc = 100 Gm 3 cc = 100 Gm	37
X	3.79	4.86	10.21	11.45	35.70	37.60	2/12/32 2/13/32	6 cc = 200 Gm 6 cc = 200 Gm	37

intravenous injections of a copper preparation during the last sixteen days. This patient had lived for several months on a diet composed essentially of crackers or bread and tea. She received an adequate diet for eighteen days in the hospital and was able to continue it satisfactorily during her entire period of treatment. This fact must be considered in evaluating the effect of the iron medications used.

The patient in case 23 received some iron during the course of pregnancy, but the observations recorded begin with intensive treatment one week post partum.

The patients in cases 13 and 14 were first treated with a liver fraction for use in secondary anemia (Whipple).<sup>3</sup> The results obtained with

this treatment are shown in tables 3 and 3 *A*, together with the results obtained in another patient (case 34) treated by the same means

The results of treatment of six patients with varying doses of ferric citrate are shown in tables 4 and 4 *A*. The patient in case 31 had a severe cold at the onset of treatment, which continued for two weeks and recurred again in three weeks. Improvement as shown in the table

TABLE 2—*Record of Patients Treated with Ferric Ammonium Citrate*

Case	Red Blood Cells, Millions per C Mm		Hemoglobin, Gm per 100 Cc		Blood Iron, Mg per 100 Cc		Daily Dose Iron Salt, Gm	Number of Days Treated	Comment
	Initial	Final	Initial	Final	Initial	Final			
13	4.74	5.07	7.90	11.38	25.90	37.30	0.9*	70	See tables 3 and 3A, case 13, for previous treatment; final red blood cell count recorded was made at end of 35 day period
14	4.62	4.87	11.06	14.39	36.23	47.10	1.0*	70	See tables 3 and 3A, case 14, for previous treatment
15	3.72	4.93	6.49	8.83			1.0†	49	
16	2.37	4.94	4.42	11.59	16.47	44.50	1.0†	91	Profuse catamenial flow last two weeks
17	3.56	4.77	7.18	14.03	24.30	44.20	1.0†	84	Thyroid substance, 0.13 Gm daily
18	3.91	5.33	4.83	13.52	18.18	42.50	1.0†	91	
19	2.97	5.14	4.83	11.73	15.75	36.60	1.0†	105	Inadequate diet before and during treatment, 120 Gm yellow bone marrow daily for 42 days previously
20	4.29	5.51	5.24	13.25	20.00	46.70	1.0†	133	See text regarding previous iron treatment
21	4.56	4.92	11.87	14.49	42.30	46.09	2.0†	56	
22	4.39	5.06	8.00	13.25	26.70	42.70	3.0*	63	
23	4.72	5.10	8.97	13.52	27.50	43.40	3.0*	70	Record starts one week post partum
24	4.68	5.38	7.87	13.25	24.50	43.80	3.0*	42	See tables 3 and 3A for previous intravenous therapy
25	4.59	5.08	9.52	12.83	36.49	40.48	3.0*	35	See tables 3 and 3A for previous intravenous therapy
26	4.40	5.39	5.52	11.04	17.77	36.50	6.0†	49	
27	3.85	4.43	10.63	13.66	34.70	44.40	6.0†	42	
28	5.38	5.35	11.59	14.03	38.90	45.00	6.0*	56	

\* Ferric ammonium citrate given in capsule form as prepared by Lederle Laboratories

† Ferric ammonium citrate given in solution

was probably definitely retarded during this time, but after an interval of time had elapsed and the infection had cleared up improvement took place more rapidly, the hemoglobin increasing in five weeks by 2 Gm or an average of 54 mg per day. These figures are not shown in the table. One other patient treated with ferric citrate but for whom the results are not shown in the table improved very slowly during the time that she had a chronic sinus infection with frequent acute exacerbations.

For purposes of comparison, there is a record of the results following the use of pills of ferrous carbonate shown in table 5 *A*. In this table are also included the results in patients who received liver extract



(fraction G of Cohn) with iron, which was shown previously to be ineffective in the production of hemoglobin and is therefore not taken into account. In table 6 *A* are similarly recorded the observations of the results obtained with ferrous carbonate and whole liver. Some of the data contained in tables 5 *A* and 6 *A* have been shown in different form in previous communications.<sup>4</sup> The minimal doses of ferric

TABLE 2A—Detailed Record of Changes in the Hemoglobin of

Case	Initial			Increase in									
	Red Blood Cells	Hemo globin	Blood Iron	7 Days	14 Days	21 Days	28 Days	35 Days	42 Days	49 Days	56 Days	63 Days	70 Days
13	4 74	7 90	25 90	1 06	0 55	1 10	3 30	3 48					
Per day				151 5	39 9	52 4	117 9	99 4					
14	4 62	11 06	36 23	1 34	0 06	—0 68					2 54		3 33
Per day				191 4	4 3	—32 0					45 4		47 5
15	3 72	6 49		1 10	1 65	2 48			0 56	2 34			
Per day				157 1	117 8	118 2			12 3	47 7			
16	2 37	4 42	16 42	0 69	2 34	2 07	3 45	3 68	3 82	5 38	4 69	5 65	5 93
Per day				98 6	167 1	98 5	123 2	105 1	91 0	109 7	83 6	89 4	84 7
17	3 56	7 18	24 30	0 41	0 27	2 89	3 58	4 00	4 83	4 83	4 41	5 65	4 96
Per day				59 6	19 39	137 5	128 0	114 3	115 1	98 6	78 7	89 4	70 8
18	3 91	4 83	18 18	0 69	2 48	3 04	2 76	3 45	5 93	4 69	5 80	6 49	6 35
Per day				98 6	177 2	144 8	98 6	98 5	141 1	95 7	103 6	103 0	90 7
19	2 97	4 83	15 75	0 41		1 38	2 48		3 86	4 40	4 00		4 55
Per day				59 6		65 7	88 6		91 9		71 4		65 0
20	4 29	5 24	20 00	—0 27	1 25	1 11	3 87	3 04			4 42	4 83	5 32
Per day				—38 6	98 4	32 7	138 3	87 1			79 0	76 8	78 9
21	4 56	11 87			1 24				0 83	1 65	2 62		
Per day					88 5				19 7	36 8	46 8		
22	4 39	8 00	26 70	0 69	3 04	3 59	3 04	4 83	4 70	4 28	4 70	5 25	
Per day				98 6	217 5	171 0	108 6	138 0	111 9	87 3	84 0	83 4	
23	4 72	8 97	27 50			2 62	2 62			2 99		3 73	4 55
Per day						124 8	93 6			61 0		59 2	65 0
24	4 68	7 87	24 50	0 82	2 33	4 41	4 93	5 72	5 38				
Per day				117 2	166 2	209 9	176 0	158 0	128 1				
25	4 59	9 52						3 31					
Per day								94 5					
26	4 40	5 52	17 77		0 69		2 35	2 76	4 83	5 52			
Per day					49 3		93 9	78 9	115 1	112 7			
27	3 85	10 63	34 70			1 33	2 83		3 03				
Per day						63 4	101 1		72 1				
28	5 38	11 50	38 90	0 97	0 97	1 80	1 93	2 35	2 38	2 26	2 49		
Per day				138 6	69 3	85 6	68 9	67 1	56 7	46 1	44 4		
Averages				0 72	1 41	2 09	3 10	3 64	3 65	3 83	3 96	5 26	5 03
Per day				102 9	101 2	99 4	111 4	104 1	93 1	77 3	70 6	83 5	71 9

\* The gain in hemoglobin at intervals of seven days is shown in grams, the gain per day, in milligrams

ammonium citrate appear to be distinctly more effective than similar doses of ferric citrate and about the same as pills of ferrous carbonate, when given in doses containing essentially the same amount of iron.

Although improvement in the blood was more satisfactory in those patients receiving the larger doses (3 Gm daily of ferric ammonium citrate) than in those receiving the smaller ones (1 Gm daily of ferric ammonium citrate), the difference in effect is not directly proportional to the amount of iron ingested.

In a previous paper<sup>1</sup> the lack of effectiveness of liver extract (Cohn fraction G)<sup>12</sup> in the treatment of secondary anemia in man was noted. Whipple and his associates<sup>3</sup> have prepared a liver fraction which they have found to be effective in producing hemoglobin when given by mouth to dogs made anemic by bleeding. Three patients were treated by means of such a liver fraction without added iron, and the results

*Patients Treated with Ferric Ammonium Citrate as in Table 2*

Hemoglobin*									Final			Total Gain		
77 Days	84 Days	91 Days	98 Days	105 Days	112 Days	119 Days	126 Days	133 Days	Red Blood Cells	Hemo globin	Blood Iron	Red Blood Cells	Hemo globin	Blood Iron
									5 07	11 38	37 30	0 33	3 48	11 40
									4 87	14 39	47 10	0 25	3 33	10 87
									4 93	8 83		1 21	2 34	
5 93 77 0	6 48 77 1	7 17 78 7							4 94	11 59	44 50	2 57	7 17	28 03
5 67 73 4	6 90 82 1								4 77	14 08	44 20	1 21	6 90	19 90
6 21 80 7	7 45 88 7	8 69 95 4							5 33	13 52	42 50	1 42	8 69	24 32
4 69 60 9		4 83 53 1		6 90 65 7					5 14	11 73	36 6	2 17	6 90	20 85
	6 08 72 3		7 32 74 6	8 15 77 5	7 73 69 0	7 59 63 7		8 01 60 2	5 51	13 25	46 70	1 22	8 01	26 70
									4 92	14 49		0 36	2 62	
									5 06	13 25	42 70	0 67	5 25	16 09
									5 10	13 52	43 40	0 38	4 55	15 90
									5 38	13 25	43 80	0 70	5 38	19 30
									5 08	12 83		0 49	3 31	
									5 39	11 04	36 50	0 99	5 52	18 73
									4 43	13 66	44 40	0 58	3 03	9 70
									5 35	14 08	45 0	-0 03	2 49	5 59
5 62 73 0	6 72 80 0	6 89 75 7	7 32 74 6	7 53 71 6	7 73 69 0	7 59 63 7		8 01 60 2					5 64	17 48

are recorded in tables 3 and 3 A. In one of the patients (case 34) improvement in the blood occurred at a rate which might be expected with the use of a minimal dose of an iron salt. Very slight improvement was noted in the other two (cases 13 and 14). The liver extract used in case 34, tested for its iron content, was found to contain approxi-

<sup>12</sup> Cohn, E. J., Minot, G. R., Fulton, J. F., Ulrichs, H. F., Sargent, F. C., Weare, J. H., and Murphy, W. P. The Nature of the Material in Liver Effective in Pernicious Anemia, *J. Biol. Chem.* **74**: 69 (July) 1927.

mately 110 mg of iron in the daily dose used. That used in cases 13 and 14 contained only about 9 mg in the daily dose. The observed effect of these extracts in the treatment of human secondary anemia is probably entirely dependent on the iron content of the extract. Similar conclusions have been reached by Cheney and Niemand<sup>13</sup>

In tables 3 and 3 A are recorded also the results obtained in two patients following the intravenous injection of iron hydroxide. Both patients improved to some extent, although in one instance the alteration in diet may have been largely responsible for the improvement noted (case 24). Further treatment by injections of iron and of copper had to be omitted because of the occurrence of reactions following the injection. The reactions consisted of a rush of heat to the face with flushing and dizziness lasting for a few minutes, followed by

TABLE 3—*Record of Patients Treated with Secondary Anemia Liver Fraction (Whipple) or Intravenous Injections of Iron Hydroxide*

Case*	Red Blood Cells, Millions per Cc Mm		Hemoglobin, Gm per 100 Cc		Blood Iron, Mg per 100 Cc		Number of Days Treated	Treatment
	Initial	Final	Initial	Final	Initial	Final		
13	4.76	4.74	8.94	7.90	29.24	25.90	56	Whipple fraction prepared from 240 Gm liver daily by mouth
14	4.99	4.62	10.38	11.06	34.01	36.23	70	Whipple fraction prepared from 200 Gm liver daily by mouth
34	4.10	4.67	9.11	12.42	34.50	43.80	49	Whipple fraction prepared from 1,000 Gm liver daily by mouth
24	2.14	4.68	4.55	7.87	17.60	24.50	77	FeOH <sub>2</sub> , † 3 cc daily intravenously
25	4.63	4.59	9.25	9.52	34.20	36.49	28	FeOH <sub>2</sub> , 3 cc daily intravenously

\* The patients in cases 13, 14, 24 and 25 were later treated with ferric ammonium citrate. See tables 2 and 2A.

† This patient received injections of copper also during last sixteen days of treatment.

faintness. The effects of subsequent treatment of these two patients with ferric ammonium citrate are shown in tables 2 and 2 A (cases 24 and 25). Although there would appear to be some value in iron administered parenterally, it probably has no advantage over that taken by mouth, especially if one considers the number of injections used and the inconvenience and expense to the patient. Difficulty in the ingestion of a sufficient amount of iron is rare indeed.

Several miscellaneous substances prepared for use in the treatment of anemia were each tried in one or two cases with little or no effect when compared to that subsequently obtained with the use of a simple iron salt. In view of the satisfactory results which may be obtained with the simple iron salts in even moderate doses and the striking results observed with the use of an iron salt together with the intramuscular

13 Cheney, G., and Niemand, F. The Treatment of Secondary Anemia with "Secondary Anemia Liver Extract" and Iron, *Am J M Sc* **184** 314 (Sept.) 1932

injection of liver solution, there would seem to be little indication for the use of complicated preparations, many of which are distinctly more expensive and more difficult to take. With the use of the simple non salts which are generally contaminated with copper and the ready availability of copper in the diet as generally advised in the treatment of anemia,<sup>14</sup> the question of the need for added copper in the treatment of anemia of the adult is of academic rather than of practical importance.

A condensed summary of the various forms of treatment is also presented in charts 1, 2 and 3. Since there was considerable variation in the different periods of treatment, in order to make a fair comparison all have been considered for an interval of sixty-three days. In the evaluation of the various forms of therapy, especially when comparing

Chart 1

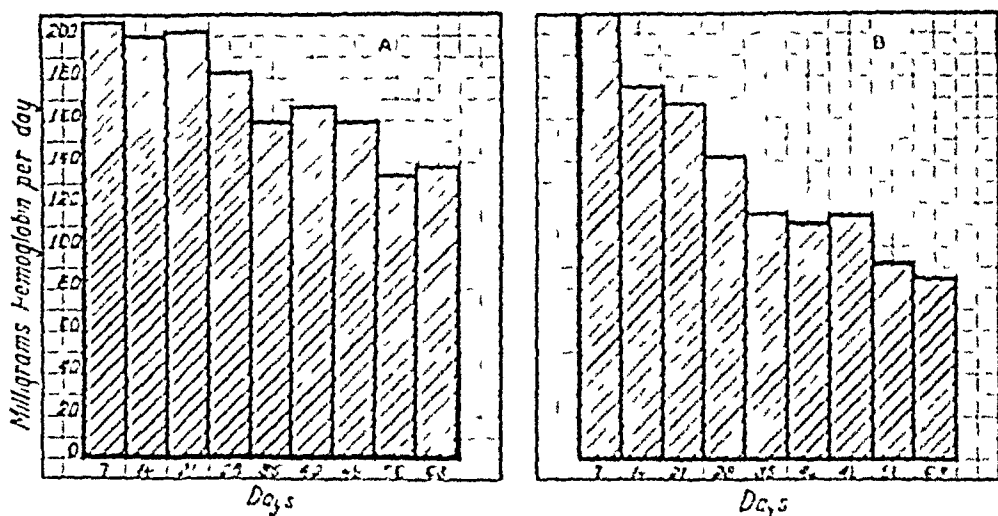


Chart 1—In *A* are given the averages for nineteen patients treated with solution of liver extract (Lederle) intramuscularly and ferric ammonium citrate by mouth (table 1, I). Seven of this group were treated after the paper was presented for publication, and data showing the rate of improvement in them are not recorded in tables 1 and 1, I. In *B* are given the averages for seven patients treated with whole liver and ferrous carbonate (table 6, I). Each vertical column in the charts represents the total average daily gain of hemoglobin in the patients of each group observed at seven day intervals.

the effects obtained with whole liver and iron (ferrous carbonate) with those obtained with intramuscular injection of solution of liver extract (Lederle) and iron (ferric ammonium citrate), it should be noted that the average ingestion of whole liver for sixty-three days was approxi-

14 Minot, G. R., and Murphy, W. P. Treatment of Pernicious Anemia by a Special Diet, *J. A. M. A.* 87:470 (Aug. 14) 1926. Murphy, W. P., and Minot, G. R. A Special Diet for Patients with Pernicious Anemia, *Boston M. & S. J.* 195:410 (Aug. 26) 1926.

mately 14,000 Gm (32 pounds), whereas the maximum amount of solution of liver extract injected over the same period represented the material obtained from not more than 1,000 Gm (22 pounds) of liver (ten 3 cc vials of liver extract). Since the clinical results obtained with ferrous carbonate compare favorably with those obtained with ferric ammonium citrate when equivalents of iron are used, and since the majority of the patients receiving the solution of liver extract belong to the chronic chlorotic type and probably respond less readily to treatment than do those with anemia resulting from chronic hemorrhage as in the group receiving whole liver, the superiority of the combination of intramuscular injections of solutions of liver extract together with ferric ammonium citrate administered by mouth is demonstrated.

TABLE 3A—Detailed Record of Changes in the Hemoglobin of Patients Treated with Secondary Anemia

Initial			Increase in Hemo											
Red Blood Cells	Hemo globin	Blood Iron	7 Days	Per Day	14 Days	Per Day	21 Days	Per Day	28 Days	Per Day	35 Days	Per Day	42 Days	Per Day
4 76	8 94	29 24	-1 10	-157 2	-0 56	-40 0	0 51	24 3	0 03	1 0				
4 99	10 38	34 01			-0 22	-15 7	-0 07	-3 3	1 15	41 0	1 12	32 0	0 32	7 6
4 10	9 11	34 50	1 10	157 2	1 65	117 9			1 65	59 0			2 21	52 6
2 14	4 55	17 60	0 42	60 0	0 85	60 7	0 85	40 4	1 52	54 3	2 21	63 2	1 25	29 7
4 63	9 25	34 20	1 38	197 1			1 65	78 5	0 27	9 64				

† The gain in hemoglobin at intervals of seven days is shown in grams, the gain per day, in milligrams.  
‡ The patients in cases 13, 14 and 34 were treated with secondary anemia liver fraction (Whipple), those in cases 1 and 23, with iron hydroxide intravenously.

### CLINICAL RESULTS

When considered as to speed of recovery, the general clinical effect observed and the increase in blood, improvement has been most striking in that group of patients who received intramuscular injections of the solution of liver extract (Lederle) together with ferric ammonium citrate by mouth. The rapidity of improvement noted in this group may be best illustrated by means of a comparison (table 7) of the effect of the various forms of treatment used. In this table are recorded the averages of the total gain in hemoglobin in grams and whole blood iron in milligrams in the patients of each group as shown in the six preceding tables called *A*. In the last column is also recorded the average daily gain in hemoglobin, expressed in milligrams. Each of the figures in this group was obtained by dividing the total average gain for each group by the total number of days during which the patients of the same group were observed. The varied results indicated by a comparison of these figures are borne out by all of the data obtained in studying the various groups. The average daily gain of 153.2 mg of hemoglobin per

day in the group treated with the solution of liver extract intramuscularly together with ferric ammonium citrate by mouth represents almost twice as great an average daily gain as was observed with any other form of treatment. There are no figures available from similar observations in man with which these may be compared. Strauss and Castle<sup>15</sup> treated the anemia of pregnancy with "large doses" of iron (ferric ammonium citrate) and found a daily average increase in hemoglobin of 0.65 per cent, or 101.4 mg. calculated on the basis of 15.6 Gm. of hemoglobin which is equivalent to 100 per cent by the method used (Sahli<sup>16</sup>). Using full doses of liver or kidney together with iron in dogs made anemic by bleeding, Whipple<sup>17</sup> recorded the production of 140 Gm. of hemoglobin in a fourteen day period. No such gains as

*Fraction (Whipple) or Intravenous Injections of Iron Hydroxide as in Table 3*

Per Day	% Days	Per Day	63 Days	Per Day	70 Days	Per Day	77 Days	Per Day	Initial			Total Gain		
									Red Blood Cells	Hemo- globin	Blood Iron	Red Blood Cells	Hemo- globin	Bleed- ing
	-1.04	-18.5							4.74	7.50	2.90	-0.02	-1.01	-
21.6	0.89	15.0	0.81	12.8	0.68	0.7			4.62	11.06	6.26	-0.37	0.68	2
17.6									3.67	12.42	4.50	0.57	7.71	9
	1.25	22.16	1.8	21.0	2.04	4.4	5.2	15.1	4.08	7.87	24.50	2.51	1.72	6
									4.9	9.32	6.90	-0.01	0.27	2

this have been made, even for short periods of time, in the patients treated by the various means herein discussed.

Even in those patients who, at least for a time, received only the intramuscular injections of the liver extract, subjective improvement was notable in spite of little or no increase in the hemoglobin level. The different amounts of iron ingested, so far as the dose used is concerned, seems not to have influenced the rate of improvement considerably and can hardly be considered responsible for the difference in the improvement noted in this group as compared with the group treated only with ferric ammonium citrate. As has been observed following the use of liver extract parenterally in the treatment of pernicious anemia,<sup>3</sup> a striking increase in appetite was noted following the injection of the liver solution and a gain of weight occurred in almost every instance.

15 Strauss, M. B., and Castle, W. B. The Etiology and Treatment of Anemia of Pregnancy, *Lancet* 1:1198 (June 4) 1932.

16 Castle. Personal communication.

17 Whipple, G. H. Experimental Anemias, Diet Factors and Related Pathologic Changes of Human Anemias, *J. A. M. A.* 91:863 (Sept. 22) 1928.

Indeed, it is difficult to picture the striking changes which have occurred during the course of treatment as just outlined. A description of the change which occurred during the course of treatment of a patient by a physician in Boston and not included in the table will give one an idea of the result to be expected<sup>18</sup>

#### REPORT OF CASE

A widow, aged 71, anemic for many years, was visited in April because of pallor, weakness and a severe productive cough. There had been bleeding from hemorrhoids for many years in the past, but none had occurred for several years. She was confined to bed, but there was no fever. An examination showed marked pallor, emaciation, generalized arteriosclerosis and moderate enlargement of the heart. The hemoglobin was 35 per cent (Tallqvist), red blood cell count, 2,568,000, and white blood cell count, 3,800. The red blood cells were small generally, with marked variation in shape. On April 18, treatment with 3 Gm of ferric ammonium

TABLE 4—*Record of Patients Treated with Ferric Citrate*

Case	Red Blood Cells, Millions per Cc Mm		Hemoglobin, Gm per 100 Cc		Blood Iron, Mg per 100 Cc		Daily Dose Iron Salt, Gm	Number of Days Treated	Comment
	Initial	Final	Initial	Final	Initial	Final			
29	3.92	4.92	6.76	11.73	23.81	39.60	1*	49	Started day after operation salpingoophorectomy
30	4.81	4.80	10.63	11.73	32.89	37.31	1*	56	
31	4.64	5.36	7.87	11.59	27.60	35.20	1*	91	Frequent colds during early part of treatment
32	4.81	5.44	8.80	14.08	25.50	43.10	1.2†	49	Started day after hemorrhoidectomy
33	3.76	5.05	10.90	15.18	36.20	46.90	3.0†	49	Ferric ammonium citrate during final 14 days
19	4.56	4.99	10.90	11.45	35.90	36.50	3.0†	49	Inadequate diet before and during treatment

\* Ferric ammonium citrate given in solution

† Ferric ammonium citrate given in capsule form as prepared by Lederle Laboratories

citrate daily and intramuscular injections of solution liver extract was started. Three injections were given at four day intervals, each dose being 3 cc derived from 100 Gm of liver. On May 5, the patient was up and about, she had no cough and stated that she felt very well. The hemoglobin was 50 per cent (Tallqvist), red blood cell count, 2,946,000, and white blood cell count, 5,200. Three more injections were given at weekly intervals, and the iron was continued. On May 29, the hemoglobin was 65 per cent (Tallqvist), red blood cell count, 5,584,000, and white blood cell count, 8,200. No further injections were given, and on June 18, the hemoglobin was 80 per cent (Tallqvist), and the red blood cell count, 5,200,000. The patient was doing her usual work and stated that she had not felt so well for ten years.

Data concerning several other patients similarly treated, which is not being shown in the tables, may be discussed briefly.

The first one, a young woman treated by another Boston physician,<sup>19</sup> had noticed weakness and pallor, and tired easily. When, seen in November, 1931, the hemo-

18 Data supplied by Dr W W Barker of Dorchester, Mass

19 Data supplied by Dr Lyman Hoyt of Boston

globin was 70 per cent (Tallqvist), and the red blood cell count, 3,900,000. The red blood cells showed marked variation in size and shape, with achromia. For five months the patient received over 2 Gm of pills of ferrous carbonate daily, and on April 6, 1932, the hemoglobin was unchanged, the red blood cell count, 3,000,000, and the appearance of the cells, essentially as noted previously. She was

Chart 2

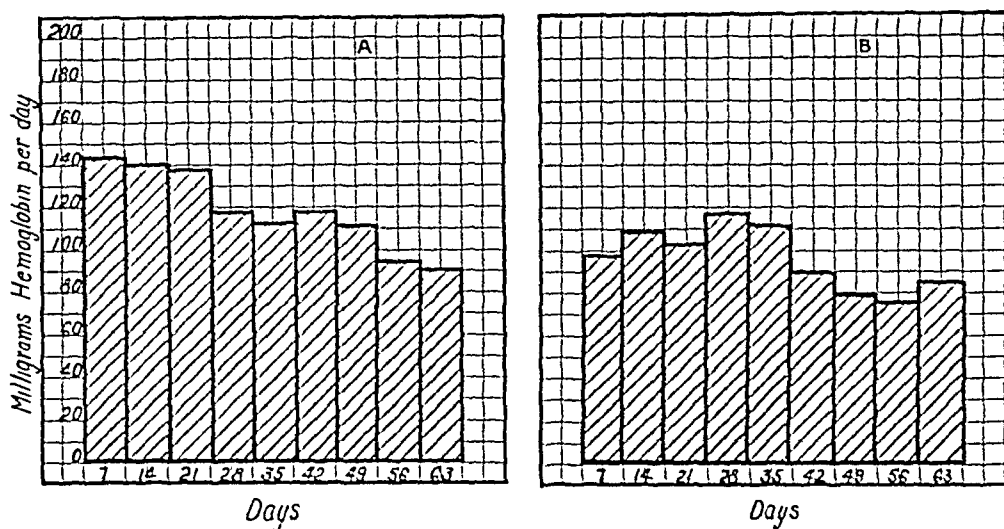


Chart 2—In *A* are given the averages of fourteen patients treated with pills of ferrous carbonate, U S P (table 5 *A*), in *B*, the averages for sixteen patients treated with ferric ammonium citrate (table 2 *A*)

Chart 3

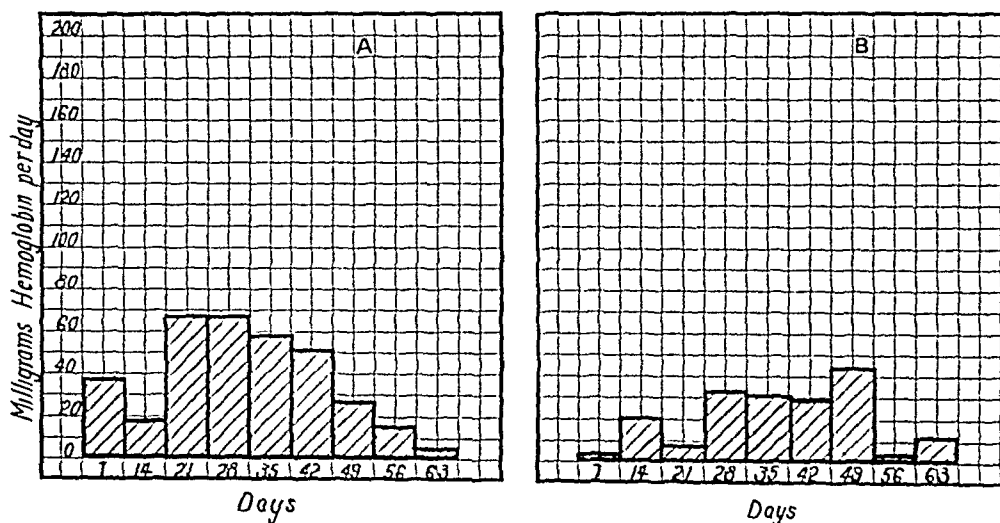


Chart 3—In *A* are given the averages for six patients treated with ferric citrate (table 4 *A*), in *B*, the averages for three patients treated with liver extract for secondary anemia (Whipple) (table 3 *A*)

then given an injection intramuscularly of 3 cc of solution of liver extract prepared from 100 Gm of liver, on each of three successive days. The pills of ferrous carbonate were continued. On April 14, the hemoglobin was 80 per cent (Tallqvist), and the red blood cell count, 4,536,000, the cells were essentially normal in appearance, and the patient stated that she felt very much better.



Another patient entered the hospital in a state of extreme weakness, with a hemoglobin level of 3.31 Gm, and 2,610,000 red blood cells. There was a large palpable mass in the right lower quadrant and loss of blood from the bowel, roentgen evidence of involvement of the intestine by tumor was interpreted as a carcinoma. The patient received ferric ammonium citrate, 3 Gm daily, and an injection of solution of liver extract intramuscularly at weekly intervals, until her blood was examined again five weeks later, at which time the hemoglobin was 5.80 Gm and the red blood cell count 3,760,000. Her strength had increased proportionately with the change in her blood.

A fourth patient had been observed elsewhere for a period of ten years because of anemia and hypothyroidism. During the ten year period she took, intermittently, liver extract by mouth, ventriculin, iron, and at times thyroid substance. During this time the red blood cell count rose above 4,000,000 cells per cubic millimeter on only a few occasions, generally varying between 3,500,000 and 4,000,000. On admission to the hospital, the patient presented the picture of

TABLE 4A—Detailed Record of Changes in the Hemoglobin

Initial			Increase in Hemogl														
Red Blood Cells	Hemo globin	Blood Iron	7 Days	Per Day	14 Days	Per Day	21 Days	Per Day	28 Days	Per Day	35 Days	Per Day	42 Days	Per Day	49 Days	Per Day	
3.92	6.76	23.81			0.34	24.2			1.93	68.9	2.21	63.1			4.97	101.4	
4.81	10.63	32.89	0.14	—20.0	0.28	—20.0			1.10	39.2	0.96	27.4	1.38	32.8	2.62	53.0	
4.64	7.87	27.60					0.69	32.8	0.82	29.3	1.65	47.2	1.24	29.5	1.79	36.5	
4.81	8.80	25.50	0.38	—54.3	0.86	61.3	0.11	—5.2	2.58	92.2			4.50	107.2	5.28	107.8	
3.76	10.90	36.20	0.55	78.7	0.55	39.3	2.21	105.2	2.21	79.0	3.18†	90.9	4.00	95.4	4.28	87.4	
4.56	10.90	35.90			—0.41	—29.2	—0.69	—32.8	—0.27	—9.9					0.55	11.2	
Average			0.01	1.40	0.21	15.0	0.52	25.0	1.39	49.6	2.00	57.1	2.78	66.2	3.25	66.3	

The gain in hemoglobin at intervals of seven days is shown in grams, the gain per day, in milligrams. The dose was changed to the same amount of ferric ammonium citrate.

obesity, thick features, constipation and anemia. The hemoglobin was 12.28 Gm, the red blood cell count, 4,300,000 per cubic millimeter of blood, the basal metabolic rate, minus 23 per cent, and the weight 98.2 Kg. With injections of solution of liver extract, 3 cc prepared from 100 Gm of liver at four and five day intervals, ferric ammonium citrate, 3 Gm daily, doses of thyroid substance varying from 0.015 to 0.045 mg daily, and a diet containing 1,200 calories, the blood rose within twelve days to a hemoglobin level of 14.49 Gm and a red blood cell count of 4,700,000, where it remained until discharge at the end of thirty days, at which time the basal metabolic rate was minus 16 per cent and the weight 94 Kg, and the bowels were acting essentially normally.

The last patient to be discussed was first seen at the Boston Lying-In Hospital during her eighth month of pregnancy with a severe degree of anemia. The hemoglobin level at that time was 6.35 Gm, the red blood cell count, 3,690,000 per cubic millimeter, and the whole blood iron, 18.12 mg per hundred cubic centimeters of blood. Ferric ammonium citrate crystals had been given for about a week with slight change in the blood level. The patient was then given injections of 3 cc of solution of liver extract prepared from 100 Gm of liver at four or five day intervals, and daily by mouth 3 Gm of ferric ammonium citrate in capsules. Her blood level rose in twenty-four days to 10.9 Gm of hemoglobin and 4,420,000 red blood cells, the blood iron rose to 39.5 mg, and by thirty days post partum,

to 13.52 Gm of hemoglobin, 5,090,000 red blood cells and 44 mg of whole blood iron. Her general condition improved steadily up to the time of discharge from the hospital.

The five cases reported are examples of the types of problems in anemia commonly encountered by the physician in which most pleasing results may be expected from the combination treatment suggested.

## COMMENT

The effectiveness of iron in the treatment of anemia of the hypochromic type has been known for many years, and even in the time of Bland<sup>20</sup> the need for large doses was recognized. Such men as Christian,<sup>21</sup> Lichtenstein,<sup>22</sup> Meulengracht,<sup>23</sup> Osler,<sup>24</sup> Minot<sup>25</sup> and others

in Patients Treated with Ferric Citrate as in Table 4

												Final			Total Gr	
obin *												Red	Hemo	Blood	Red	Hemo
56	Per	63	Per	70	Per	77	Per	84	Per	91	Per	Blood	globin	Iron	Blood	globin
Days	Day	Days	Day	Days	Day	Days	Day	Days	Day	Days	Day	Cells			Cells	
1 10	19 6											4 92	11 73	39 60	1 00	4 97
0 69	12 3	2 48†	35 4	2 89	38 8	3 03	36 1	3 72	40 9	3 72	38 0	4 80	11 73	37 31	-0 01	1 10
												5 36	11 59	35 20	0 72	3 72
												5 44	14 08	43 10	0 63	5 28
												5 05	15 18	46 90	1 29	4 28
												4 99	11 45	36 50	0 43	0 55
0 89	15 8															3 32

noted the improvement which will follow the administration of adequately large doses of iron in a simple form. There is lacking in the literature, however, data obtained as the result of controlled observations on the treatment of secondary anemia in man, which would indicate the relative value of the more common iron salts, of substances other than iron or various means of administering these. Reports as to

20 Bland, P. Sur les maladies chlorotiques, et sur un mode de traitement spécifique dans ces affections, *Rev méd franç et étrang* **1** 337, 1832.

21 Christian, H. A. A Sketch of the History of the Treatment of Chlorosis with Iron, *M. Libr & Hist J* **1** 176 (July) 1903.

22 Lichtenstein, A. *Jahrb f Kinderh* **38** 387, 1918.

23 Meulengracht, I. Large Doses of Iron in the Different Kinds of Anemia in a Medical Department, *Acta med Scandinav* **58** 594, 1923.

24 Osler, W. *Modern Medicine*, ed 3, Philadelphia, Lea & Febiger, 1927, vol 5, p 66.

25 Minot, G. R. Treatment of Anemia, in Christian, H. A., and Mackenzie, J. *Oxford Medicine*, New York, Oxford University Press, 1928, vol 2, pt 2, p 649.

the value of the various treatments which have been suggested from time to time for the treatment of human anemia have led to much confusion owing to several factors, some of which are as follows

TABLE 5A—Detailed Record of Changes in the Hemoglobin of Patients Treated with Pills of

Initial			Increase in												
Red Blood Cells	Hemo-globin	Blood Iron	7 Days	Per Day	14 Days	Per Day	21 Days	Per Day	28 Days	Per Day	35 Days	Per Day	42 Days	Per Day	49 Days
4 08	4 14	19 40	0 97	133 5	3 59	256 6	5 38	236 3	6 07	217 0	6 35	181 5	6 49	154 4	
4 46	5 24	18 10	1 52	217 1	3 45	246 5	3 73	177 7	4 14	147 9					5 69
3 89	8 14	28 00	1 24	177 1	1 38	98 5	2 49	118 6	2 49	80 9	2 90	54 2	3 07	73 1	
4 09	6 62	21 30	0	0	1 52	108 5			2 63	93 8					
2 96	7 59	25 20	2 07	395 8			4 00	190 5							
2 16	4 14	16 10			0 69	49 3							5 80	138 1	7 45
5 24	7 04	29 20	0 55	78 6	1 10	78 5	2 34	111 2	2 21	78 8	2 76	62 3	4 48	106 6	5 10
2 56	4 28	15 75	1 10	157 0	2 62	186 9			6 62	236 5	7 31	209 1	8 55	201 1	9 52
4 99	6 07	20 20	0 42	60 0	3 04	217 1	4 69	223 5					6 90	164 4	
4 25	6 90	23 60	0 97	138 5	3 31	236 4	2 76	131 4	2 07	71 8	3 31	94 5	3 59	85 5	
3 42	6 07	25 90			0 55	39 3	2 49	118 6	2 21	78 8			3 87	92 2	2 76
4 00	8 56	31 40	0 27	38 5			2 07	98 5	2 34	83 6	3 06	87 4			
3 48	6 90	24 20					1 38	65 7							4 42
4 88	7 73	24 90			0 69	49 3	1 10	52 3	2 90	103 6			2 48	59 1	3 31
Averages			1 01	144 6	1 99	142 4	2 94	140 4	3 37	119 4	4 28	114 9	5 02	119 4	5 46

The gain in hemoglobin at intervals of seven days is shown in grams, the gain per day, in milligrams. These case numbers are used in previous papers.<sup>4</sup> The patients in the last six cases also received fraction G of Cohn

TABLE 6A—Detailed Record of Changes in the Hemoglobin in

Initial			Increase in												
Red Blood Cells	Hemo-globin	Blood Iron	7 Days	Per Day	14 Days	Per Day	21 Days	Per Day	28 Days	Per Day	35 Days	Per Day	42 Days	Per Day	49 Days
2 98	6 76	26 60	2 07	295 8			3 45	168 6	3 59	128 2	3 45	98 5	4 14	98 5	3 87
3 05	4 55	17 60							4 01	143 1	2 90	82 9	3 73	106 6	5 52
3 35	3 45	16 90	3 45	493 0	4 83	344 9	6 21	296 1	6 21	222 1	6 90	197 0			7 59
3 93	5 52	19 00	0 69	98 5	1 38	98 5	3 17	150 9	3 17	113 3	3 45	98 5			6 21
2 96	7 73	26 30	0 96	137 2	3 59	256 6	4 00	190 5	4 00	143 0	4 55	130 0			4 00
3 56	9 80	28 50	0 27	38 5	0 69	49 3	1 65	78 5	1 93	63 9	2 07	59 1	2 62	74 8	
2 20	4 55				1 80	128 6	2 63	125 2	4 83	172 6	5 39	154 0	7 04	167 6	6 90
Averages			1 48	212 6	2 45	175 6	3 52	168 8	3 96	141 6	4 10	117 1	4 38	111 7	5 65

The gain in hemoglobin at intervals of seven days is shown in grams, the gain per day, in milligrams. These case numbers were used in previous papers.<sup>4</sup> The results are obtained by the Kennedy method and are not comparable with others

1 The control observations are inadequate in order to establish a knowledge of the results which may be expected under uniform circumstances. Cases of anemia of similar origin must be used and data recording the effect thereon of a uniform and simple iron preparation should be available for comparison.

2 The periods of observation are of too short duration to get the maximum effect. The figures in the tables suggest that in the majority of instances the maximum effect of treatment occurs between the second

*Ferrous Carbonate (18 Gm) Alone or Together with Liver Extract (Cohn Fraction G)*

Hemoglobin *											Final			Total Gain		
Per Day	56 Days	Per Day	63 Days	Per Day	70 Days	Per Day	77 Days	Per Day	84 Days	Per Day	Red Blood Cells	Hemo globin	Blood Iron	Red Blood Cells	Hemo globin	Blood Iron
					7 45	106 5					5 31	11 59	41 80	1 23	7 45	22
115 6	6 21	111 1			6 90	98 6			7 73	92 1	5 14	12 97	37 50	0 68	7 73	19
									3 87	46 1	4 56	12 01	41 40	0 67	3 87	13
	4 83	86 3									5 00	11 45	39 00	0 91	4 83	17
											4 64	11 59	44 00	1 68	4 00	18
152 1	7 31	150 8									4 09	11 45	37 00	1 93	7 31	20
104 1	4 14	73 9	4 55	72 3	4 14	70 1	4 97	64 4	4 55	53 6	5 49	11 59	33 15	0 25	4 55	8
194 5			10 07	160 0							4 44	14 35	43 80	1 88	10 07	28
							5 94	77 0			5 50	12 01	41 60	0 51	5 94	21
							3 31	43 0			4 50	10 21	44 40	0 25	3 31	20
56 3							5 11	66 5			5 34	11 18	39 90	1 92	5 11	14
			3 17	50 3							4 97	11 73	39 30	0 97	3 17	7
90 3	4 42	78 8									4 98	11 32	35 10	1 50	4 42	10
67 6											4 73	11 04	41 90	-0 15	3 31	17
111 5	5 38	96 1	5 93	94 3	6 16	88 0	4 83	62 7	5 38	63 9					5 36	17

*Patients Treated with Ferrous Carbonate (18 Gm), and Whole Liver*

Hemoglobin *											Final			Total Gain		
Per Day	56 Days	Per Day	63 Days	Per Day	70 Days	Per Day	77 Days	Per Day	84 Days	Per Day	Red Blood Cells	Hemo globin	Blood Iron	Red Blood Cells	Hemo globin	Blood Iron
78 9	3 59	64 1							4 42	5 36	4 99	11 18	37 3	2 01	4 42	10
112 8	6 49	115 7	6 77	106 2			7 32	95 1	8 70	102 6	4 85	13 25	41 10	1 80	8 70	23
154 6											5 23	11 04	36 70	1 38	7 59	19
126 7											5 30	11 73	38 00	1 32	6 21	19
81 6	5 24	93 4	4 41	70 1							5 01	12 14	38 60	2 05	4 41	12
					3 03	43 3					4 74	12 83	41 40	1 18	3 03	12
140 9											4 10	11 45		1 90	6 80	
115 9	5 11	91 1	5 59	88 1	3 03	43 3	7 32	95 1	6 56	78 1					5 89	16

and fourth weeks after the beginning of treatment. It is therefore apparent that a change of therapy made during this interval would lead to results which may be misinterpreted. The second form of treatment would then receive credit for results actually produced by the first form of treatment.

3 The effect of any form of treatment on a specific type of anemia in animals cannot be interpreted as indicating its value in the anemias of man, the origin of which may be entirely different

In carrying on the study which is reported in this and two preceding papers,<sup>4</sup> an effort has been made to utilize patients for treatment who have anemia of the hypochromic type, either idiopathic, combined with dietary inadequacies, or produced by chronic loss of blood. In a few instances, alveolar abscesses or pyorrhea have been present, but they were usually treated during the course of medication. Occasionally other complications such as arthritis or gallbladder disease have been present. In these and similar instances, one may probably expect less rapid improvement than in a similarly treated patient without complication.

TABLE 7—*Clinical Results*

	Total Average Gain in Hemoglobin, Gm	Total Average Gain in Whole Blood Iron, Mg	Hemoglobin Calculated from Whole Blood Iron, Gm	Average Daily Gain Over Whole Period, Mg
Secondary fraction	1.33	3.84	1.17	2.28
Intravenous iron	1.79	4.59	1.40	34.2
Ferric citrate	3.32	9.45	2.88	58.0
Ferric ammonium citrate	5.64	17.48	4.61	73.7
Ferrous carbonate	5.36	17.25	5.26	82.4
Ferrous carbonate and whole liver	5.89	16.36*	5.36*	92.1
Solution liver extract intramuscularly and ferric ammonium citrate	6.47†	19.57	5.97	153.2†

\* These results were obtained by the Kennedy method and are not comparable with others.

† This figure is based on results observed in nineteen patients, seven of whom were treated after the paper was presented for publication, and data showing the rate of improvement are not recorded in tables 1 and 1A.

It has been the policy to advise the patient to take an adequate well balanced diet, essentially as advised by Minot and Murphy.<sup>14</sup> A few of the patients were unable to take an entirely adequate diet owing to their financial status, and in these patients improvement has been less satisfactory than in those able to take the regulation diet. Although a few of the patients were started on treatment during a period of observation in the hospital, they have all been ambulatory during the greater part of the period of treatment.

From a comparison of the observations recorded in earlier papers with those of this paper, it appears that the most striking improvement occurred in those patients who received intramuscular injections of solution of liver extract (Lederle) together with iron by mouth and in those who ingested rather large amounts (240 Gm.) of whole liver<sup>1</sup> daily together with iron. This suggests that the iron ingested is utilized more efficiently when given in conjunction with a substance which will build the "stroma" (Whipple<sup>26</sup>) of the red blood cells. That such a condition actually occurs is very well shown in those patients who

26 Whipple, G. H. Pigment Metabolism and Regeneration of Hemoglobin in the Body, *Arch. Int. Med.* 29:711 (June) 1922.

received the intramuscular injections of solution of liver extract alone for a period of time and then with iron by mouth. In some cases the red blood cell count was seen to increase following the injections, but only after the addition of iron therapy did the hemoglobin level rise, and then rapidly. That whole liver will increase particularly the stroma of the red blood cells in anemia other than pernicious is suggested by the data recorded in a previous paper.<sup>1</sup> Reznikoff<sup>27</sup> has shown also that iron is retained in a normal subject to a greater degree when injections of a liver solution are given intramuscularly than without its use.

This need on the part of the blood-forming organs to have stroma-building material available in order that the iron may be utilized to the best advantage is comparable to the situation which occurs during the treatment of pernicious anemia by means of intramuscular injections of a solution of liver extract, except that in the latter case the iron supply becomes inadequate during the rapid production of red blood cells and improvement will be greater if iron is supplied during the course of treatment. Owing to the high iron content of whole liver and the green vegetables, such a situation does not often arise when a patient with pernicious anemia is treated with whole liver and the anemia diet.

In those patients in whom the principal form of therapy was a simple iron salt there appears to be some difference between the effectiveness of the three salts used. The patients receiving pills of ferrous carbonate or ferric ammonium citrate showed better responses than did those receiving ferric citrate. Although the smaller or minimal doses of iron were sufficient in practically every instance to cause reasonably satisfactory improvement, there is likely to be a lag in the formation of hemoglobin as the normal level is approached. In those patients who received the larger doses of iron, improvement was somewhat more rapid and more nearly normal levels were reached than in those receiving less iron, but the rate of improvement was not directly proportional to the amount of iron given.

Although ferric ammonium citrate and ferrous carbonate have been effective when given in amounts sufficient to supply approximately from 170 to 180 mg of iron daily, such a dose is probably a minimally effective one and not sufficient to produce as satisfactory improvement in the blood of the majority of patients as may be possible with larger doses. On the other hand, doses of the iron salts supplying approximately 1,000 mg of iron daily have not been more effective than doses supplying 500 mg of iron. The optimal and most economical dose of these iron salts for the majority of patients is therefore that amount which will supply daily 500 mg of iron.

<sup>27</sup> Reznikoff, P. Iron Metabolism Studies, *Proc. A. Soc. Clin. Investigation* 11: 807 (July) 1932.

An important feature of the studies carried out has been the lack of evidence to suggest that special combinations of iron with other substances for administration by mouth have any definite value over the use of the simple iron salts in the treatment of the types of anemia treated. The special preparations containing iron are apparently utilized less effectively than the simple iron salts, often more disagreeable to the patient, and invariably more expensive.

Although the number of patients treated in each separate group may be considered insufficient to establish beyond doubt the actual value of each type of therapy employed, there can remain little doubt but that large amounts of iron should be used in preference to the minimal dose in order to obtain optimal results in a larger percentage of patients, and that improvement of both patient and blood will take place more rapidly and to a more satisfactory degree when iron therapy is combined with intramuscular injections of a solution of liver extract or perhaps with whole liver by mouth. Large amounts of liver, however, are taken less readily by patients with this type of anemia than by those with pernicious anemia.

It is hoped that the results recorded in the three papers may be of value as a control group for those who may carry on the treatment of anemia with other substances.

#### SUMMARY

The results of treatment by various means of a group of patients with anemia of the hypochromic type are recorded.

A comparison of the effect on the blood of the types of treatment carried out and reported in this and two previous papers is made and the following conclusions drawn:

1. Treatment by means of intramuscular injections of solution of liver extract (Lederle) together with adequate doses of iron (ferric ammonium citrate) by mouth is the most effective, although the combination of large doses of whole liver and iron by mouth is very effective but less readily used.

2. Of the various substances other than whole liver which were given by mouth, ferric ammonium citrate and pills of ferrous carbonate U S P were about equally effective and outranked the others in blood-building effect. The optimal dose of these salts is that which supplies daily 500 mg of iron (ferric ammonium citrate, 3 Gm, pills of ferrous carbonate, 5.4 Gm).

3. Iron hydroxide used intravenously proved to be moderately effective but without advantage over the iron administered by mouth.

Isabel Howard gave expert technical assistance.

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# AVITAMINOSIS IN NATIVES OF RHODESIA

## TREATMENT OF EPIDEMIC SCURVY BY THE INTRAVENOUS INJECTION OF CITRUS

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Since the cause of most deficiency diseases has been established, and since an efficacious and easily available cure has been found to exist in the observance of what is now regarded as a protective and well balanced diet, there is a strong tendency to regard these diseases as belonging to the bygone prescientific ages. This, together with the fact that ill health may be produced by deficiency of a food factor in amounts much smaller than those necessary to create the typical full-blown picture associated with its lack, explains why the deficiency syndromes are more common than their diagnosis. It is to be expected, therefore, that deficiency syndromes may occur in persons existing for any considerable length of time on a restricted diet, either therapeutic or voluntary, or as a result of dietary eccentricities.

Davidson<sup>1</sup> reported three cases of deficiency disease in patients on a diet prescribed for ulcer. He called attention to the fact that in the overwhelming enthusiasm for controlling obvious functional derangements by dietetic measures, the maintenance of the patient on a diet containing the necessary accessory food factors is often ignored.

A diet prescribed for colitis,<sup>2</sup> consisting of rice, milk, eggs, white meats and broth, led to the development of scurvy after eleven months. Mettier, Minot and Townsend<sup>3</sup> reported nine cases of avitaminosis following restriction of food. Martin<sup>4</sup> reported a severe scorbutic condition in a patient who had been under dietetic and alkaline treatment for duodenal ulcer for six months, the condition was precipitated by an attack of influenza, thus illustrating, as many others have shown, the importance

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Work done while a medical officer of the Rhodesian Railways, 1931

1 Davidson, P B. The Development of Deficiency Disease During Therapeutic Diets, J A M A **90** 1014 (March 31) 1928

2 Immerman, S L. Scurvy Following a Restricted Diet in Colitis, J A M A **94** 1757 (May 31) 1930

3 Mettier, S R, Minot, G R, and Townsend, W C. Scurvy in Adults, Especially Effect of Food Rich in Vitamin C on Blood Formation, J A M A **95** 1089 (Oct 11) 1930

4 Martin, H E. Scurvy Following an Ulcer Diet, Lancet **2** 293 (Aug 8) 1931



of auxiliary factors in the causation of deficiency syndromes Bullowa,<sup>5</sup> Giorgi,<sup>6</sup> and Swanson<sup>7</sup> are among contributors to the literature who show the importance of being on the outlook for such diseases if the diet in any way diverges from the normal, or if nutritional disturbances arise from coexisting disease Swanson reported the only case I was able to find in the literature in which scurvy developed as a result of continued vomiting during pregnancy Hyperemesis, commencing two months prior to the onset of purpuric phenomena, had been preceded by a diet high in vitamins The onset of scorbutic features was sufficiently dramatic to suggest the presence of one of the blood dyscrasias, but examination of the blood and the subsequent course of events showed it to be a case of scurvy The disturbance of the mineral metabolism under these circumstances may have been a factor in the severity of the purpura

Cases in which deficiency disease assumes epidemic proportions are of particular interest since they illustrate more effectively the variety and the number of contributing causes, as well as the ease with which such outbreaks may be controlled with institution of proper treatment Both of these principles as well as many aspects of faulty nutrition are well demonstrated by an outbreak of scurvy among the native laborers in the railroad reconstruction camps in Southern Rhodesia during 1931 A description of the prevailing conditions and of the mode of living of the native (Kaffir) follows

The natives concerned, of which there were about 10,000, were drawn principally from the Northern Rhodesian territories, in some instances several hundred miles from the area under consideration, and were employed as laborers on railroad reconstruction from Victoria Falls to a point 75 miles south They were distributed in a series of camps along this stretch, which served as their temporary homes while under contract

In his native surroundings the Kaffir leads an undisturbed existence By disposition he is leisurely, unselfishly allowing his women folk and pickaninnies to indulge in tilling the soil or herding the few cattle or small flock of sheep and in preparing the national beverage of "kaffir beer" "The noble male must hunt, the woman may dig in the dirt," applies here very well Hence his food supplies fluctuate with fortune, with the seasons and with his ingenuity in trapping game, and he is

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5 Bullowa, J G M Self-Induced Avitaminosis Beriberi and Scurvy, *Medicolegal Aspects, Period for Development and for Cure*, M Clin North America **10** 959 (Jan) 1927

6 Giorgi, E Epidemic Scurvy, *Pediatrics* **29** 66 (Jan 15) 1921, abstr, J A M A **76** 689 (March 5) 1921

7 Swanson, C N Scurvy Complicating Vomiting of Pregnancy, J A M A **88** 26 (Jan 1) 1927

often saved by the grace of good government from dying of starvation. But despite periods of deprivation, fully developed deficiency syndromes are rare among the Kaffirs when in their native environment. In lean times they seek food and occupation from the European settlers, at other times recruiting agents gather large numbers of them to seats of mining and construction activities, where the weak and the aged have often to be included in order to capture the services of their more robust brother. This is a very unfortunate but apparently unavoidable state of affairs, and explains largely why the average native under consideration is of rather poor physique.

The distance to the nearest railway center is in many cases considerable, and the Kaffir travels most often on foot, carrying all his personal belongings, with but little food for himself and his wife and family who accompany him. It is conceivable, then, that when he arrives at his destination he is all but starved.

A consideration of the etiology of deficiency diseases in general would include some of the important predisposing factors already mentioned. The natives who had not already manifest signs of scurvy would soon succumb to the effects of what, to them at any rate, is hard physical labor, in totally new surroundings, with the contributing factor of mental depression induced by what probably is their first encounter with the hardships of life.

Should this impart the idea that native laborers are loaded with overburdening tasks, I should like to dispel such impressions by saying that the government appoints labor inspectors for their protection and their interests. But it cannot be too strongly emphasized that in a previously undernourished person the extra metabolism attendant on work hastens the exhaustion of vitamins, so that soon a latent deficiency disease will appear. Even in the days of Captain Cook's<sup>8</sup> expeditions it was known that longer hours of sleep were important in combating the effects of supplies low in vitamins and the onset of the sailors' dreaded disease.

Once the Kaffir is employed, he is fed according to government regulations, which include all the essentials of what has come to be regarded as a protective diet, and which in fact is a very liberal diet. But at the onset he is usually somewhat averse to eating the green vegetables of the white man, and until he has learned their value, he is likely to discard them. The one criticism of the diet is its high carbohydrate content. As McCarrison<sup>9</sup> and others have shown, lack of

<sup>8</sup> Angus, T. S. Captain Cook's Hygiene, Brit. M. J. **2** 1233 (Dec. 31) 1927.

<sup>9</sup> McCarrison, Robert. Studies in Deficiency Disease, New York, Oxford University Press, 1921.

balance in diet is almost as important as the restriction of vitamins in the production of deficiency disease

The important sources of vitamins in the government ration scheme were green vegetables, meat and beans (which are sprouted prior to cooking), but the native was as likely to discard these as he was to render them valueless by excessive cooking. The natives were also allowed to make a certain amount of kaffir beer (or *leting*), a brew in which sprouted cereal (usually kaffir corn or "*sorghum vulgare*") is used as malt. It is of low alcoholic content and contains a small amount of vitamin C. In a study of scurvy, as it occurs on the Rand Gold Mines in South Africa, Delf<sup>10</sup> emphasized its value in the diet of the native. The same investigator has shown that about 200 cc of the brew was effective in protecting monkeys from developing scurvy. At least it can be said that the right of brewing his beer makes the native a happier individual, and its consumption at least induces a state of artificial euphoria in one neither highly pleased with life nor over-cheerful in surroundings which are so totally unlike those of his natural environment.

Besides the specific deficiency in vitamins and the accessory factors, such as previous undernourishment, muscular exertion and mental depression already mentioned, any condition which lowers the general resistance, increases the metabolic burden or adds to nutritional defects will hasten the onset of manifest scurvy or add to the seriousness of the clinical picture.

Hardly a native escapes infection with intestinal parasites, especially ankylostomiasis. Darling<sup>11</sup> asserted that 75 per cent of microscopic examinations of stools revealed infection, and treatment with vermifuge leads to recovery of worms or their ova in about 98 per cent of cases. Dysentery, both amebic and bacillary, and indeterminate forms of diarrhea are common enough to duplicate the already high morbidity accounted for by recurrent attacks of malaria. The relation between avitaminosis and infections has been widely considered in the literature. McCarrison,<sup>12</sup> among others, has provided much evidence of lowered resistance to infection as a result of deprivation of vitamins. More especially is the integrity of the covering epithelial structures affected, allowing infection to occur more readily, so that a specific anti-infective factor has found its place in the classification of vitamins.

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10 Delf, E. M. Studies in Experimental Scurvy, with Special Reference to the Antiscorbutic Properties of Some South African Foodstuffs, *Lancet* **1** 576 (March 25) 1922.

11 Darling, quoted by Manson-Bahr, P. H. Scurvy in the Tropics in Manson Tropical Disease, ed. 8, New York, William Woods & Company, 1925, p. 337.

12 McCarrison, Robert. Some Surgical Aspects of Faulty Nutrition, *Brit M J* **1** 966 (June 6) 1931.

It is equally true that scurvy is often precipitated by infective febrile illnesses, probably due to the fact that the increased metabolism associated with fever exhausts more rapidly the supply of vitamin, much in the same way as exercise does. In this respect, then, it is analogous to the facts known about the decreased action of insulin under similar circumstances, but scurvy in itself appears to cause an elevation of the metabolic rate. This observation was made by Knipping and Kowitz<sup>13</sup> who found that a previously increased basal metabolic rate in cases of avitaminosis was reduced to normal by the addition of orange juice to the diet.

Lind<sup>14</sup> reported an outbreak of scurvy among the inmates of an asylum in Victoria (Australia) which illustrates the part infection plays in the causation of scurvy. In this instance there had been no alteration in the diet of the patients for years, but an infectious condition (the nature of which was not determined) caused a febrile illness and led to an outbreak of the disease in epidemic form.

Race, age and sex enter into the consideration of the etiology of scurvy. One subtribe of the great Barotsi race, known as the Mulhivali, contributed about 80 per cent of the total number of scorbutic patients at the construction camps. This race presents several interesting features. First, they are regarded as the most savage of Northern Rhodesian tribes. Second, as a tribal custom their teeth are filed into sharp, peg-shaped structures. The dental decay following this procedure would certainly account for the marked scorbutic features of their gums, even if the disease is mild.

Women and children were noticeably free from scurvy, probably for once the general order of life was reversed, and it was they who led the leisurely life while the father of the family was earning the daily bread. A final factor worthy of mention was the fact that native employers had depended on the use of crude lime juice as a prophylactic agent against deficiency disease, an extract which has been proved experimentally by Chick, Hume, Skelton and Smith<sup>15</sup> to be almost entirely devoid of antiscorbutic properties. The same writers record some interesting facts relative to the arctic expeditions of the nineteenth century. Thus the crew of "The Investigator," 1850, enjoyed remarkable immunity from scurvy for the first and second years, whereas those of a subsequent expedition on "The Alert and The Discovery" 1875,

13 Knipping, H. W., and Kowitz. Untersuchungen über die Avitaminose beim Menschen, München med Wchnschr 1 46 (Jan 12) 1923

14 Lind, W. A. T. Some Interesting Details of an Outbreak of Scorbutus, M. J. Australia 2 107 (Aug 9) 1919

15 Chick, Harriette, Hume, E. Margaret, Skelton, Ruth F., and Smith, Alice H. (A) Experimental Inquiry. The Relative Content of Antiscorbutic Principle in Limes and Lemons, (B) Historical Inquiry, Lancet 2.735 (Nov 30) 1918

suffered severely at the end of the first winter spent in the arctic regions, for although the former used lemon juice, the latter were supplied with limes

The pathologic changes are essentially the occurrence of hemorrhages of varying degrees into various parts of the body, the nature of which is not entirely clear. From the hematologic standpoint, anemia with a corresponding reduction in hemoglobin is the only constant symptom, with relative absence of the usual evidences of secondary anemia, suggesting a condition of relative aplasia of the bone marrow. Piney<sup>16</sup> corroborated this observation. Platelets do not appear to be reduced. From a study of thirteen cases of scurvy Shattuck<sup>17</sup> claimed that the platelet counts, bleeding time, coagulation and clot retractility are normal. Bedson<sup>18</sup> studied the platelets both in man and in monkeys and guinea-pigs, and suggested that hemorrhages occur during transient reduction of the platelets, although the figures quoted as obtained by him on repeated examinations both before and after scorbutic symptoms are present do not justify his assumption, since they all fall well within the normal range. Mettier, Minot and Townsend have studied the bone marrow obtained by biopsy from the sternum and claim that it resembles the picture seen in secondary anemia. After treatment such studies indicate marked reactivity of the marrow which then contains numerous mitotic figures and increased numbers of nucleated erythrocytes. It appears then that anemia is due not only to undernutrition, loss of blood and intercurrent infections, but also to inadequate function of the bone marrow dependent on a chronic lack of vitamin C. On instituting treatment, a reticulocyte response is noted which commences on the third day, reaches its peak about the eighth day and then declines. Figures as high as 99 per cent reticulocytes were recorded under these circumstances. The leukocytes in uncomplicated scurvy are normal.

Experiments have been carried out indicating absence of metabolic disturbances except such changes as can be accounted for by inanition attendant on the end-stages of advanced scurvy. Humphreys and Zilva<sup>19</sup> reported that there is no deviation from the normal in the absorption or retention of calcium and phosphorus before or during the development of scurvy in guinea-pigs until the last stages of the

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16 Piney, Alfred. *Recent Advances in Hematology*, ed 2, London, J & A Churchill, 1928.

17 Shattuck, G. C. *Scurvy with Reference Especially to Adults*, J. A. M. A. **90** 1861 (June 9) 1928.

18 Bedson, S. P. *The Blood Picture in Scurvy, with Particular Reference to the Platelet*, Brit. M. J. **2** 792 (Nov. 12) 1921.

19 Humphreys, F. E., and Zilva, S. S. *Metabolism in Scurvy. III. The Absorption and Retention of Calcium and Phosphorus by Guinea-Pigs*, Biochem. J. **25** 579, 1931.

experiment, when all physiologic functions of the animal become deranged by the disease. The experiments of Howard and Ingvaldsen<sup>20</sup> carried out to determine whether an explanation of the pathogenesis of scurvy could be found in aberrations of the mineral metabolism, failed to reveal evidence sufficiently significant to draw such conclusions. That there should be rapid nitrogen loss in scurvy is to be expected, and this was found to be the case by the last named investigators as well as by Caridroit,<sup>21</sup> and by Nagayama and Sato.<sup>22</sup> Blood sugar levels,<sup>23</sup> glycogen content<sup>24</sup> of the liver and the carbohydrate metabolism as a whole are normal, whereas lipid metabolism<sup>25</sup> is only disturbed in the final stages of the experiment.

### SYMPTOMS

The main features of fully developed scurvy in the native need be mentioned only briefly here. The facies is characteristic. His complexion is muddy, as if he were unwashed. In an epidemic, a native who walks with a limp is to be strongly suspected of being scorbutic. Careful examination proved this to be the case in many instances. The gums show the characteristic sponginess and bleed easily. However, it should be remembered that when the teeth are in good condition the changes in the gums may be in abeyance until the late stages of the disease. The relation between avitaminosis and dental caries has been commented on in the current literature. Suffice it to mention here that carious teeth were extremely common among natives afflicted with the disease, and this is of unusual interest as the African aborigines are credited with as nearly perfect teeth as are possible to be found.

Hemorrhages in various parts form the prominent feature of the scorbutic subject. The petechiae around the hair follicles on the legs,

20 Howard, C. P., and Ingvaldsen, T. The Mineral Metabolism of Scurvy of the Monkey, *Bull. Johns Hopkins Hosp.* **28** 222 (July) 1917.

21 Caridroit, F. Variation de l'excrétion azotée (azote total urinaire) au cours du scorbut expérimental, *Compt. rend. Soc. de biol.* **90** 1379 (May 24) 1924, abstr., *J. A. M. A.* **83** 226 (July 19) 1924.

22 Nagayama, T., and Sato, N. Studies in Experimental Scurvy. Nitrogen Metabolism of the Animal Fed on Vitamin C Free Diet, *J. Biochem.* **10** 27 (Oct) 1928.

23 Nagayama, T., Machida, H., and Takeda, Y. Studies in Experimental Scurvy. Carbohydrate Metabolism of Animal Fed on Vitamin C Free Diet, *J. Biochem.* **10** 17 (Oct) 1928.

24 Koga, Y. Studies in Experimental Scurvy, Contribution to Study on Carbohydrate Metabolism of Guinea Pigs Fed on Vitamin C Free Diet, *J. Biochem.* **11** 461 (Jan) 1930.

25 Nagayama, T., and Tagaya, T. Studies in Experimental Scurvy. Lipid Metabolism of Guinea Pigs Fed on Vitamin C Free Diet, *J. Biochem.* **11** 225 (Oct) 1929.

of the earlier stages, naturally cannot easily be detected in the black skin. Extensive bleeding into the subcutaneous, subperiosteal and intermuscular spaces leads to the severe crippling and painful condition associated with the disease, whereas the larger weight-bearing joints and mucous membranes may be similarly affected. I recall one case which, in addition to the usual evidences of scurvy, presented all the classic signs of a mediastinal tumor. Treatment of the scorbutic condition led to dramatic relief of symptoms and the disappearance of all the signs which had led one to suspect a tumor of a more serious nature. Similarly, scorbutic hemorrhages may lead to confusing symptoms and erroneous diagnoses, especially when the usual signs of scurvy are not prominent or not looked for. Sammis<sup>26</sup> reported a case of scurvy in which a subdural hemorrhage was the cause of death. The spinal cord may be similarly involved, whereas abdominal emergency conditions may be diagnosed when hemorrhage occurs into the bowel. Such a case is described by Foote<sup>27</sup>. A child, aged 2½ years, had symptoms of abdominal spasms and passed blood-streaked stools, the gums were normal and although the clinical picture closely simulated intussusception, exploration was delayed until purpuric spots developed, when a diagnosis of scurvy was made. Complete and rapid recovery followed the usual antiscorbutic treatment. The skin overlying hematomas becomes hard and leathery to the touch. The condition of the blood has been mentioned.

Gastro-intestinal symptoms were not frequently complained of, but it is possible that the deficiency of vitamins may have accounted for at least some of the cases of indeterminate diarrhea. Mackie and Chitre<sup>28</sup> found that the colon of the monkey is very sensitive to deficiency of vitamins, especially vitamin C, which causes a condition varying from local congestion and thickening of the mucous membrane to one indistinguishable from ulcerating and sloughing dysentery.

The time required for scorbutic signs to become manifest naturally varies greatly. Dyke<sup>29</sup> reported an outbreak among the men of the South African Native Labor Corps in France during the war, three or four months after their arrival. About 40 per cent of the particular group were affected, and here the predisposing factors must have been somewhat similar to those affecting the natives under consideration. In the latter group, I became associated with the work after the construction

26 Sammis, J. F. Scurvy with Cerebral Hemorrhage, *Arch. Pediat.* **36** 274 (May) 1919.

27 Foote, R. R. Scurvy Simulating Acute Intussusception, *Brit. M. J.* **1** 1035 (June 19) 1926.

28 Mackie and Chitre, quoted by McCarrison. *Brit. M. J.* **1** 966 (June 6) 1931.

29 Dyke, H. W. Outbreak of Scurvy in the South African Native Labour Corps, *Lancet* **2** 513 (Oct. 19) 1918.

had been in progress for about five months. At that time 80 per cent of persons reported to be ill had scurvy, and the total number of natives affected in varying degrees must have been 60 per cent of those in the camps.

The onset is, as a rule, insidious, with loss of weight, progressive anemia and a feeling of stiffness in the legs. Either at this stage or when definite purpuric manifestations are present, other signs and symptoms may be present which are difficult to dissociate from true scurvy and which are actually included by some writers in the scorbutic syndrome. Many complained of hemeralopia. Bryson<sup>30</sup> claimed that night blindness is (1) an early or initial symptom of scurvy, (2) the main symptom, the other symptoms being slighter than usual, or (3) a symptom coexisting with fully developed scurvy.

Deficiency edema, mild or advanced, was even more frequently met in sufferers from scurvy. This is of the nature of hunger edema of infants, and it is not always possible to elicit edema until correct diet initiates such extensive diuresis as to transform what seemed like a well-fed child into a veritable skeleton. Walgren<sup>31</sup> has mentioned the invisible edema of scurvy based probably on an increased state of permeability of the capillary walls, but it is more likely that hunger edema is due to a decreased level of plasma protein as in nephrosis and in plasmapheresis. During periods of food deprivation, several factors in the diet may be responsible for deficiency syndromes, and under such conditions it may be impossible to determine which individual components of the clinical picture are due to a particular deficiency. That the plasma proteins may be low in hunger edema has been proved by Liu, Chu, Wang and Chung,<sup>32</sup> who studied the problem in cases of edema of the nutritional type occurring in the inmates of an orphanage. In the cases studied the total plasma protein was as low as 3.46 per cent (the albumin fraction being 1.43 per cent in the same case). Until it can be shown that the edema fluid contains an increased amount of proteins, one cannot depend on an increased capillary permeability for the explanation of a particular variety of edema. Here there is not the same massive loss of the albumin fraction in the urine as in nephrosis, and the only reasonable assumption is that the plasma proteins become depleted as a result of protein deficiency in the diet. The last named workers showed also that the food proteins have a qualitative as well

30 Bryson, Alexander. Night-Blindness, in Connection with Scurvy, Roy London Ophth Hosp Rep **2** 40, 1859.

31 Walgren, Arvid. Zur Symptomatologie und Pathogenese des Oedema scorbuticum invisible, Ztschr f Kinderh **31** 35, 1922.

32 Liu, S. H., Chu, H. I., Wang, S. H., and Chung, H. L. Nutritional Edema. I. Effect of Level and Quality of Protein Intake on Nitrogen Balance, Plasma Proteins and Edema, Proc Soc Exper Biol & Med **29** 250 (Dec) 1931.



as a quantitative relation to hunger edema. Thus the amount of vegetable protein for each kilogram of body weight required to build up plasma protein and to reduce edema is twice as much as the amount of animal protein necessary to secure the same effects.

An interesting parallelism may be drawn between the hemorrhagic features and edema occurring in scurvy on the one hand and those occurring in the anaphylactoid types of purpura on the other, although the mechanism in the two groups of cases is naturally different.

In potential scorbutic subjects, wounds (which were common about the legs) became chronic sores, and until the scurvy is treated this so-called tropical ulcer refuses to heal. This is an entirely different condition from the well known tropical sore of leishmaniasis. The tropical ulcer commences in an abrasion or wound, and is apparently of nonspecific origin, although numerous organisms and spirochetes have been incriminated. It does not respond to antiprotozoal medications administered either locally or intravenously.

Finally, Hess<sup>33</sup> claimed that latent scurvy may be elicited by the tourniquet test.

The prevalence of vitamin C deficiency naturally raises the possibility of other forms of deficiency disease. The possible relationship to dental caries, infections, night blindness and hunger edema has already been considered. Although conjunctivitis was frequently seen, no direct etiologic relation to such a condition can be claimed to exist. Keratomalacia was never encountered.

The pains complained of in the limbs and in many cases the presence of edema naturally lead one to suspect beriberi, but in rare instances only was there any evidence of true peripheral neuritis. The consumption of beans and whole wheat undoubtedly affords sufficient protection against this malady.

Cases of pellagra are not infrequently reported from prisons, apparently the mental changes attendant on the disease bring the afflicted individual into conflict with the law.

Rickets is rarely encountered in South Africa.

#### TREATMENT

The treatment of scurvy falls under two headings: specific treatment and treatment of the associated pathologic conditions which do not require special mention here.

The high antiscorbutic value of the citrus fruits and the satisfactory response to their use is well known. Under ordinary conditions a simple dietary adjustment meets all requirements, and heroic procedures are

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<sup>33</sup> Hess, quoted by Manson-Bahr, P. H. Scurvy in the Tropics, in Manson Tropical Disease, ed. 8, New York, William Woods & Company, 1925, p. 337.

unwarranted and superfluous. This, then, was the method adopted at the outset. It is to be remembered, however, that the circumstances with which this account deals were somewhat different from those under which medicine is ordinarily practiced, and for completeness of narrative some of the difficulties encountered and the course resorted to are described.

The demand for fresh fruits and vegetables could be met only by importation from considerable distances, since local production of sufficient quantities was not possible. Even so the supplies were not inadequate. But the most serious obstacle was the unwillingness of the native to make use of such supplies once procured. The savage whose mind is warped by fear and superstition and who is blind to the consequences of depending solely on his traditional fare under circumstances so entirely different from his traditional mode of living cannot be readily induced to comprehend either the nature of his illness or the means to rectify it.

The treatment adopted was that carried out at one of the mine hospitals in that area,<sup>34</sup> which consisted in the intravenous administration of specially prepared and neutralized orange or lemon juice. Donaldson<sup>35</sup> has also recommended this method of treatment. Hess and Unger,<sup>36</sup> in 1918, reported on the use of neutralized orange juice intravenously in experimentally produced scurvy of guinea-pigs, claiming a more rapid response than from animals treated as controls by the usual feeding methods. As evidence of the potency of even small amounts of vitamin C when administered in this way, it should be noted that these investigators reduced the vitamin content of their extract appreciably by boiling prior to injection, and yet the recovery of the scorbutic animal was highly satisfactory. That they were fully aware of the thermolability of the antiscorbutic principle is obvious, since they demonstrated in the same series of experiments that when orange juice was submitted to an autoclave for from ten to fifteen minutes at a temperature of 110 C, most but not all of its vitamin C was destroyed. Since orange juice is an entirely unsuitable medium for growth of organisms, there is no necessity for further sterilization by boiling, provided the usual precautions are observed against contaminations.

It cannot be stated accurately how much, if at all, simple neutralization impairs the antiscorbutic value of citrus juices, but such a step

<sup>34</sup> Kerr, J. R. Personal communication to the author.

<sup>35</sup> Donaldson, quoted by Manson-Bahr, P. H. *Scurvy in the Tropics*, in Manson *Tropical Disease*, ed. 8, New York, William Woods & Company, 1925, p. 337.

<sup>36</sup> Hess, A. F., and Unger, L. J. *Experiments on Antiscorbutics*. Report of an Antiscorbutic for Intravenous Use, *Proc. Soc. Exper. Biol. & Med.* **15** 141, 1918.

would seem to be essential in their preparation for intravenous medication. Spencer<sup>37</sup> administered unneutralized orange juice to a patient with scurvy in doses of 10 cc diluted in 150 cc of physiologic solution of sodium chloride. Apart from the questionable safety of such a procedure, it is hardly a practical treatment to be used as a routine, should the necessity ever arise to administer vitamin by the intravenous route.

Attempts to place an active preparation of vitamin C on the market have failed for the most part on account of its instability. Givens and McClugage<sup>38</sup> claimed that desiccation of orange juice at a temperature of 55 to 60 C for forty minutes or more did not destroy sufficient vitamin to render the product useless. Since then many similar claims have been made, yet at present, so far as I have been able to ascertain, there is no satisfactory active principle or preparation of vitamin C suitable for intravenous administration.

Emphasizing again the limited use of an intravenous preparation for clinical purposes, the isolation of vitamin C in a pure and potent form would at least herald the advance of our knowledge of the chemistry of the vitamins. Moreover, within recent years the recognition of states of hypervitaminosis (at least with reference to vitamin D<sup>39</sup>) has been shown to be of as much importance as the recognition of the avitaminoses, and such a preparation as vitamin C would lend itself to a useful application in the field of experimental medicine. Owing to the presence of several other vitamins in the citrus juices, the extract considered here can have only limited practical application. However, that it does contain vitamin C in high concentration and that it can be used without any untoward reactions was shown by the results obtained after several thousand such injections. The method used for the preparation of the extract was as follows. The juices were expressed from fresh oranges or lemons, previously immersed in a 5 per cent phenol lotion to sterilize the skin of the fruits. The extract so obtained was filtered under aseptic conditions and then rendered neutral or slightly alkaline in reaction by the addition of 20 per cent sodium hydroxide. This was always freshly prepared and used the same day. The initial dose was 5 cc, thereafter, from 10 to 15 cc twice weekly.

In gauging the efficacy of this method and the rapidity of its action, one cannot record definite time intervals since the degree of severity of

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37 Spencer, H. A. Scurvy. Its Treatment with Raw Orange-Juice Intravenously, *South African M. Rec.* **24** 386 (Sept 11) 1926.

38 Givens, M. H., and McClugage, H. B. The Antiscorbutic Property of Fruits. I. An Experimental Study of Dried Orange Juice, *Am. J. Dis. Child.* **18** 30 (July) 1919.

39 Harris, L. J. The Mode of Action of Vitamin D. The "Parathyroid" Theory, Clinical Hypervitaminosis, *Lancet* **1** 1031 (May 14) 1932.

the disease varies so considerably in different cases. However, in comparing the group of patients treated by means of oral administration at the outset with the group treated by the intravenous method, one can definitely state that the rate of recovery was more rapid as shown by the shorter period of hospitalization when the latter form of administration was adopted. Be it said in its favor that it at least appealed to the savage mind.

#### SUMMARY AND CONCLUSIONS

The frequency of the occurrence of deficiency syndromes among patients on restricted diets for any reason is considered.

An account is given of the various factors which entered into an outbreak of scurvy among Rhodesian native laborers, and of the manifestations of this disease, as well as of associated forms of avitaminosis.

Under most conditions the oral administration of citrus fruits and fresh vegetables has been found to be highly efficient in correcting the ill effects of deprivation of vitamin C. When circumstances similar to those described arise, the intravenous use of especially prepared orange and lemon juices may be relied on as a safe and efficient method of controlling scurvy. That the vitamin C content of citrus juices is not appreciably impaired by neutralization immediately before its administration is evidenced by the rapid recovery of scorbutic patients after its use.

# BRONCHIAL DISINFECTION AND IMMUNIZATION

## II EFFECTS IN RABBITS OF INTRABRONCHIAL INJECTIONS OF VACCINES, BACTERIOPHAGE AND ANTIVIRUS

JOHN A KOLMER, M D

PHILADELPHIA

While bronchial disinfection by intrabronchial lavage with various chemotherapeutic agents would appear to be both possible and safe as determined by experiments on rabbits, and worthy of clinical trial in the treatment of bronchiectasis and other types of chronic suppurative pneumonitis,<sup>1</sup> the results of additional experiments summarized in this paper indicate that local immunization and disinfection of the bronchi by intrabronchial injections of vaccines, antiviral and bacteriophage may offer even greater therapeutic possibilities and prove worthy of clinical trial in the treatment of bronchiectasis and other types of pulmonary suppuration

Undoubtedly subcutaneous and intracutaneous injections of properly prepared autogenous vaccines are sometimes of therapeutic value in certain cases of chronic bronchitis, especially those associated with allergic asthma, but vaccine therapy has generally failed to be of any particular value in the treatment of bronchiectasis

It would appear that intrabronchial injections of vaccines and antiviral may open up a new and promising chapter in the treatment of this and other types of the chronic bronchitides if suitable experiments on rabbits show that the procedure is safe and feasible

### PHAGOCYTOSIS IN RELATION TO BRONCHIAL INFECTION

Phagocytosis is undoubtedly the chief mechanism of defense against bronchial infection and likewise the chief and possibly the sole mechanism of recovery. Therefore, anything that may safely be done to increase phagocytosis of the organisms productive of chronic bronchitis and bronchiectasis, and especially of streptococci and staphylococci may be expected to have therapeutic value

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From the Research Institute of Cutaneous Medicine and the Laboratories of the Graduate School of Medicine of the University of Pennsylvania

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1 Kolmer, J A Bronchial Disinfection and Immunization I Effects in Rabbits of Intrabronchial Injections of Various Chemical Disinfectants Arch Int Med to be published

In this connection I refer not only to phagocytosis of organisms by microphages (the polymorphonuclear leukocytes) but likewise, and possibly more importantly, to phagocytosis by macrophages with special reference to clasmatoocytes. At least the cells of the macrophage system appear to be more phagocytic in chronic infections.

In this connection the macrophages referred to are principally the monocytes of the circulating blood, the capillary endothelium, the epithelium of the aveoli of the lung and more especially the clasmatoocytes, and my interest in the latter is based primarily on the investigations of Gay<sup>2</sup> and his associates on the rôle they have apparently played in resistance to, and recovery from, experimental streptococcic pleuritis of rabbits.

While the exact origin of these clasmatoocytes, so named by Ranvier<sup>3</sup> and also designated as histiocytes and tissue macrophages, is unknown, Gay expressed the belief that they are derived from connective tissue, and his work has shown that they are mobile, actively phagocytic and undoubtedly important cells of what he has called the macrophage system.

In a study of smears of a large number of bronchial exudates secured bronchoscopically from cases of chronic bronchitis and bronchiectasis, I have experienced difficulty in recognizing the cells, but with the aid of staining with hematoxylin and eosin as well as with neutral red, as described by Gay and Morrison,<sup>4</sup> these large phagocytic ovoid cells with large eccentric or indented nuclei have been found with considerable regularity. I believe that any procedure resulting in their increase may possess therapeutic value.

#### VACCINES BY INTRABRONCHIAL ADMINISTRATION

As shown by Gay and Morrison, the intrapleural injection of sterile broth, 1 per cent egg white, 1 per cent peptone solution, acacia broth and other substances into the pleural cavities of rabbits has resulted in a great increase in these clasmatoocytes in the exudates and pleural tissues, and after seventy-two hours the changes resulted in greatly increased resistance to intrapleural injections of virulent streptococci. According to these investigators, however, the results were not due as much to what was injected as to the time element, and it has occurred to me that intrabronchial injections of vaccines made of heat-killed broth cultures of streptococci and other organisms may serve equally

<sup>2</sup> Gay, F. P. Tissue Resistance and Immunity, *J. A. M. A.* **97** 1193 (Oct 24) 1931.

<sup>3</sup> Ranvier, M. L. Des clasmatoocytes, *Compt. rend. Acad. d. sc.* **110** 165, 1890.

<sup>4</sup> Gay, F. P., and Morrison, L. F. Clasmatoocytes and Resistance to Streptococcus Infection, *J. Infect. Dis.* **33** 338 (Oct) 1923.

well in producing a local mobilization of these and other phagocytic cells

Furthermore, it may be that a vaccine administered in this manner may cause increased production of antibodies, with special reference to opsonins, by the local tissues (bronchi and parenchyma of the lungs), since it would appear that some evidence has accumulated to show that antibodies are produced primarily and principally by the tissues directly infected and antigenically stimulated. And since opsonins bear an important and essential relationship to the mechanism of phagocytosis, it has occurred to me that intrabronchial injections of autogenous vaccines prepared with broth may serve the dual purpose of increasing the macrophages of the exudates and tissues with special reference to clasmatoocytes and increasing the production of specific opsonins so vitally concerned in both microphagic and macrophagic phagocytosis

#### ANTIVIRUS BY INTRABRONCHIAL ADMINISTRATION

In this connection it is also pertinent to inquire into the possible therapeutic value of intrabronchial injections of Besredka's antiviral in the treatment of chronic bronchitis and bronchiectasis since this may be related in some respects to the artificial stimulation of clasmatoeytic phagocytosis

Antiviral is prepared by cultivating the organism in a suitable broth medium for from eight to ten days followed by Berkefeld filtration. The filtrate is designated as "antiviral," and according to Besredka<sup>5</sup> contains something which is specifically bacteriostatic and bactericidal for the organism. That is to say, if the organism is replanted in the filtrate it either fails to grow or grows but sparsely, whereas other organisms grow almost as luxuriantly as in the control broth medium. Besredka stated that the inhibiting substance is specific, thermostable and atoxic and for the want of a better term has called it antiviral. According to his experiments, it is possible to protect the lower animals against anthrax infection by first treating them with cutaneous applications of anthrax antiviral, and numerous experimental and clinical reports indicate that the application of wet dressings of staphylococcus and streptococcus antiviruses are of therapeutic value in the treatment of local staphylococcal and streptococcal infections. Since the results occur quickly, ordinarily in from twenty-four to forty-eight hours, Besredka expressed the opinion that antibody production is not involved, although he spoke of local cutaneous vaccination, while Gay<sup>2</sup> stated that the results are probably due to clasmatoeyte stimulation

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<sup>5</sup> Besredka, A. Local Immunization by Specific Dressings, edited and translated by Plotz, Baltimore, Williams & Wilkins Company, 1927

Be that as it may, there is no doubt that an organism planted in its antivirus fails to grow or grows but poorly even though it may retain its vitality and grow when subcultured into fresh broth. It may be that these effects are due to the exhaustion of specific pabulum, the accumulation of specific inhibitory metabolites, the production of specific inhibitory enzymes or the production of a virus identical with or related to what d'Herelle has designated as "bacteriophage." Here I am concerned with its probable value in the treatment of chronic bronchitis and bronchiectasis by intrabronchial injection, provided suitable experiments with rabbits indicate that it is nontoxic and safe for administration in this manner, an inquiry into its exact nature and mechanism of therapeutic activity will be left for further investigation. Indeed, Rosenthal<sup>6</sup> has already employed intrabronchial injections of antivirus in the treatment of bronchiectasis with alleged encouraging results.

#### BACTERIOPHAGE BY INTRABRONCHIAL ADMINISTRATION

Personally, I am inclined at present to the view that antivirus owes its therapeutic properties to stimulation of both microphagic and macrophagic phagocytosis along with local antibody production, but it may contain a principle directly destructive for the organism as Besredka maintains. If this is true there may be a relationship between antivirus and bacteriophage as previously stated, at all events, it would appear profitable likewise to inquire into the possible therapeutic benefit to be derived from intrabronchial injections of bacteriophage in the treatment of chronic bronchitis and bronchiectasis.

The exact nature of the Twort-d'Herelle bacteriophage, however, is unknown at the present time, d'Herelle<sup>7</sup> maintained that it is a specific ultramicroscopic living virus capable of specifically destroying living bacteria. Others regard it as a bacterial enzyme, and while its nature is in dispute there is no doubt about the phenomenon of bacteriophagy in the test tube at least. That is to say, bacteriophage is sometimes derived from living organisms, and when the latter are subsequently planted from a stock culture in a solution of it they gradually undergo lysis. In other words, when living organisms are placed in antivirus they do not proliferate and may be recovered in a living state by subcultures, when placed in potent bacteriophage, they undergo destruction by lysis. Both are specific, that is to say, exhibit these effects only on the organisms used in the preparation of antivirus or bacteriophage, and while the effects are apparently dissimilar these may be due to

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<sup>6</sup> Rosenthal, G. La cure de la dilatation des bronches et le rôle des injections intratrachéales et la trachéofistulisation emploi des boues antiseptiques, Paris méd 1 134, 1928.

<sup>7</sup> d'Herelle, F. The Bacteriophage and Its Behavior, translated by George H. Smith, Baltimore, Williams and Wilkins Company, 1930.



quantitative or other factors without necessarily involving two entirely different antibacterial substances

However that may be, my primary interest in the present connection is the possible therapeutic value of intrabronchial injections of bacteriophage in the treatment of chronic bronchitis and bronchiectasis on the basis that if this were found safe and feasible by experiments on rabbits, therapeutic results may occur either by direct lysis of the infecting organisms, by stimulating microphagic and macrophagic phagocytosis or even by the local production of antibodies with special reference to opsonins

At the outset, however, it was realized that bacteriophagic therapy involved considerable technical difficulty, especially in the preparation of suitable and potent bacteriophage for the streptococci recovered in cultures of bronchial secretions. Staphylococcus bacteriophage is easier to prepare, and that which is commercially available is frequently lytic for the staphylococci occurring in purulent bronchial exudates, but the preparation of bacteriophage for pneumococci has met with no success so far in my laboratory

#### TOXICITY OF VACCINES, ANTIVIRUS AND BACTERIOPHAGE FOR RABBITS BY INTRABRONCHIAL INJECTION

Vaccines of *Staphylococcus aureus* and hemolytic streptococci recovered in cultures of bronchial secretions, containing approximately 1,000,000,000 heat-killed cocci per cubic centimeter and preserved with 0.3 per cent cresol, were extremely well borne by rabbits receiving as much as 1 cc per kilogram of weight every two or three days for as many as twenty-four consecutive intrabronchial injections. In every instance the animals survived, maintained their weight and showed no demonstrable ill effects to either vaccine

The same was true of a second series of rabbits receiving from six to twenty-four intratracheal injections of antiviruses of the same strains prepared by cultivating the organisms in a broth medium for ten days followed by Berkefeld filtration. As much as 1 cc per kilogram of weight was injected every two or three days, and all animals survived without demonstrable ill effects

Similar results were observed with bacteriophages for both strains injected intratracheally in a similar dose of 1 cc per kilogram of weight every two or three days for a total of from six to twenty-four consecutive injections, so that it may be stated that these substances were well borne by normal rabbits by this route of administration despite the fact that the doses were purposely made extremely large according to body weight. It is true that the injections were sometimes followed in a few hours by a temporary elevation of rectal temperature along with slight but definite leukocytosis especially in those animals receiving

intrabronchial injections of the two vaccines, but these changes were usually observed only after the first to the third injection, following which it appeared that the animals rapidly acquired tolerance for all three products of each organism

Furthermore, the injections did not appear to produce more than slight amounts of bronchial exudates. Autopsy was performed several days after the last of six, twelve and twenty-four injections of each product, and the lower portion of the trachea and of the bronchi were carefully inspected along with the preparation of smears from numerous locations for cytologic examination, but in no instance were there any macroscopic evidences of pronounced bronchitis resulting from irritation due to any of the products administered

The smaller bronchi, however, frequently contained more exudate than was found in untreated controls and especially in those rabbits receiving intrabronchial injections of the two vaccines, smears stained with methylene blue (methylthionine chloride, U S P), hematoxylin and eosin and neutral red showed the presence of increased numbers of not only polymorphonuclear leukocytes but likewise of the larger cells corresponding to descriptions of the morphologic and staining characteristics of clasmatocytes. These cytologic changes were most marked, however, in smears of secretions from rabbits receiving injections of the vaccines and antiviruses, but were practically absent or much less in evidence in smears taken from animals receiving the injections of the two bacteriophages

#### PATHOLOGIC TISSUE CHANGES

Sections for histologic examination were also prepared from the trachea above the bifurcation, the lungs and kidneys of all animals

So far as the trachea and larger bronchi are concerned, there were practically no pathologic changes beyond a slight degree of hyperemia with slight edema in the submucosa of an occasional animal and especially among those receiving injections of the two vaccines

The smaller or terminal bronchi, however, sometimes showed slight but definite histologic evidences of irritation characterized by the presence of exudates on the mucosa with small peribronchial areas of cellular infiltration. The ciliated epithelium of the mucosa, however, appeared to be intact in all instances. Of course, the cellular infiltrations of the submucosa and surrounding alveoli commanded most attention, and these appeared to be composed largely of polymorphonuclear leukocytes and lymphocytes, but in many instances examination with high magnification showed larger cells which may have been clasmatocytes. Unfortunately, I could not be sure of their identity in the sections, and vital staining for their more definite identification was not employed

At any rate, it was evident that intrabronchial injections of the vaccines, antiviruses and bacteriophages were well borne by all of the animals but with slight histologic evidences of irritation, although the bronchi, particularly the smaller divisions, showed slight but definite evidences of increased cellular exudation, especially in the case of the animals receiving intrabronchial injections of the vaccines and antiviruses. These changes, however, were not uniformly distributed through the lungs but were more apparent in the right lungs and especially in the lower lobes, probably because of a wider distribution of the inocula in these locations. In no instance were there any evidences of bronchopneumonia or severer injury with abscess production, as is sometimes observed following intrabronchial injections of chemical agents previously described,<sup>1</sup> and the kidneys of all animals presented no macroscopic or microscopic evidences of injury.

#### ANTIBODY PRODUCTION BY INTRABRONCHIAL IMMUNIZATION

Preliminary opsonic and agglutination tests were made of the blood of all animals before the injections were given and repeated at intervals throughout the period of from six to twenty-four treatments. The phagocytic and opsonic indexes showed a distinct increase, especially well marked among the rabbits receiving the staphylococcus and streptococcus vaccines, although well defined individual variations in antibody response among the animals has not permitted anything more than a general statement. These results were definite in the majority of the animals after the second intrabronchial injection, while in others the effects were not clearly demonstrable until after as many as four injections had been given.

All of the animals receiving intrabronchial injections of the two antiviruses also showed an increase of opsonin for both organisms, but in general terms the amount was somewhat less than that observed in the rabbits receiving the vaccines, while the amount observed was still less in those receiving the injections of the two bacteriophages. While marked individual variations occurred, it would appear that the vaccines were most antigenic in this particular and the bacteriophages least antigenic.

Similar results were observed in agglutinin production for both organisms. These tests were technically more satisfactory and the reactions sharper and more definite. Here again the vaccines and antiviruses appeared to be more antigenic than the bacteriophages, and all three of the staphylococcus products were more antigenic than those prepared of the streptococci, furthermore, the agglutinins appeared more tardily, especially those for the streptococci, which in some instances were not definitely demonstrable until after as many as five injections had been given.

The results have clearly shown that intrabronchial injections of staphylococcus and streptococcus vaccines, antiviruses and bacteriophages result in the production of specific opsonins and agglutinins in normal rabbits

#### ACQUIRED PROTECTION BY INTRABRONCHIAL IMMUNIZATION

Additional experiments were conducted in an attempt to determine whether intrabronchial injections of vaccines and antiviruses of virulent *Staphylococcus aureus*, a hemolytic streptococcus and a type I pneumococcus afforded any protection against intrabronchial injections of broth cultures of these organisms

The vaccines of all three organisms were prepared by cultivating them in a suitable broth medium for three days followed by sterilization with 0.3 per cent cresol. They represented vaccines of chemically killed organisms along with such toxins as were produced during an incubation of three days.

The antiviruses were prepared by cultivating the organisms in broth for ten days followed by Berkefeld filtration and subculturing for sterility.

The dose of each vaccine and antivirus was 1 cc per kilogram of weight administered by intratracheal injection every two days for from three to six injections.

Controls received intratracheal injections of the sterile broth medium in the same dosage and manner and at the same time as did the experimental animals.

Especially definite evidence of acquired immunity to the type I pneumococcus was observed after as few as three intrabronchial injections of the pneumococcus vaccine and antivirus. For example, the intratracheal injection of 0.5 cc of ten hour hormone broth cultures<sup>1</sup> of this pneumococcus into control rabbits resulted in a fatal septicemia of all with positive cultures of the heart blood within forty-eight hours after inoculation. The same was true of rabbits inoculated intratracheally after receiving from two to three intrabronchial injections of sterile broth, indicating that the broth alone was without demonstrable protective value against this highly virulent pneumococcus injected intratracheally. But all of the animals receiving the intrabronchial injections of the vaccine survived when given injections with the virulent pneumococcus, as was likewise true of all animals receiving three injections of the antivirus. These results, therefore, afforded definite evidence of the fact that intrabronchial injections of type I pneumococcus vaccine and antivirus resulted in immunization against fatal infection by intratracheal inoculation with the organism, and since intrabronchial

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<sup>1</sup> Broth culture medium, presumably containing vitamins or hormones derived from living tissue and, therefore, favorable to bacterial growth.

injections of sterile broth were without these effects it is apparent that the presence of the pneumococcus and its products in the vaccine and antiviral produced specific effects

Less definite evidence, however, was secured in the case of the staphylococcus and streptococcus owing to the fact that both organisms were much less virulent for rabbits by intratracheal inoculation

Only from 20 to 50 per cent of the controls inoculated intratracheally with large amounts of twenty-four hour hormone broth cultures (2 cc) succumbed with septicemia, as was likewise true of controls receiving three preliminary intrabronchial injections of sterile broth for non-specific mobilization of microphagic and macrophagic phagocytes including clasmotocytes. However, all animals receiving three preliminary intrabronchial injections of the staphylococcus and streptococcus vaccines and antiviruses survived when inoculated intratracheally with 2 cc amounts of twenty-four hour hormone broth cultures of the respective organisms and thereby indicated some degree of acquired immunity, but since some of the controls likewise survived, the results were not as definite as those observed with the type I pneumococcus

However, it was apparent that as few as three intrabronchial injections of vaccines and antiviruses of *Staphylococcus aureus*, a hemolytic streptococcus and a type I pneumococcus resulted in engendering demonstrable degrees of acquired immunity to the three organisms which was especially well marked in the case of the pneumococcus

#### PRACTICAL APPLICATIONS

I am convinced, therefore, that it is both safe and feasible to try intrabronchial injections of autogenous vaccines, antiviruses and bacteriophages in the treatment of the chronic intractable bronchitides, bronchiectasia and other types of suppurative pneumonitis of man

Certainly it would appear from these experiments with rabbits that all three substances are extremely well borne by intrabronchial injection and that their administration by this route may be of therapeutic benefit

Autogenous vaccines and antiviruses are especially interesting in this connection because of the ease of preparation in the large amounts likely to be required. The preparation of bacteriophage is much more difficult and indeed may be impossible for some of the bacteria secured in cultures of bronchial secretions. *Staphylococcus* bacteriophage is ordinarily readily prepared and may be obtained commercially, but the preparation of streptococcus and pneumococcus bacteriophages may be difficult and indeed impossible so far as the preparation of the large amounts of actively lytic products are concerned. Furthermore, bacteriophages should not be tried until actual preliminary tests have shown that they are actively lytic in the test tube for the organisms against which they are to be employed. I believe that intrabronchial injections

of actively lytic phages may be of therapeutic benefit, but the technical difficulties of preparation may constitute an objection to their use on a large scale

Autogenous vaccines, however, are readily prepared in large amounts, and for this purpose I suggest that bronchial secretions be secured bronchoscopically in the Tucker, Cleif or other collectors and cultured in flasks of hormone broth medium suitable for the cultivation of streptococci. These may be incubated for about five days, at the end of which time fairly heavy growths will be observed. In many instances these are almost pure cultures of streptococci, but in the majority of such cultures staphylococci, pneumococci and various gram-positive and gram-negative organisms also occur with streptococci predominating. The mixed culture, however, should be used and may be diluted with sterile saline solution to give a total concentration of about 1,000,000,000 organisms per cubic centimeter. Cresol may now be added to give a total concentration of 0.5 per cent (10 cc of a stock 5 per cent solution to each 100 cc of vaccine), well mixed and incubated at 37 C for twenty-four hours when subcultures are made for sterility. This type of vaccine contains the broth and approximately 1,000,000,000 chemically killed organisms per cubic centimeter along with their exogenous toxins and, in my opinion, is to be preferred to the usual heat-killed suspensions in saline solution in order to secure the effects of the broth alone in the mobilization of both microphages and macrophages with special reference to clasmotocytes in the bronchial exudates and in the bronchial tissues for purposes of phagocytosis.

Antivirus may be prepared in exactly the same manner, except that the culture of bronchial secretions in broth is cultivated at 37 C for ten days followed by Berkefeld filtration. The clear filtrate should then be cultured for sterility and put in sterile vials or flasks in the amounts required for treatment without the addition of a preservative.

Only future clinical trial can determine the relative therapeutic effectiveness of vaccine and antivirus, personally, I expect results from both and especially from the latter.

The method of administration and dosage must likewise be determined by clinical trial and experience, but I would suggest that the ropy, mucoid secretions first be removed by lavage with the Bledsoe-Fisher hypertonic saline solution by the method of Stitt<sup>8</sup> before introducing vaccine, antivirus or bacteriophage. According to this method, 15 cc of saline solution is slowly forced through a catheter into the bronchi coincidentally with each inspiration, followed by expulsion along with the thick ropy secretions until as much as 250 cc is used. Following the last

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<sup>8</sup> Stitt, H. L. Bronchial Aspiration and Irrigation with a Hypertonic Saline Solution, *J. Med.* 8:112 (May) 1927.

washing, the vaccine, antiviral or bacteriophage may be introduced

The initial dose may be about 5 cc in order to have it retained with as wide distribution as possible. If well borne, the treatments may be given about twice a week and the doses gradually increased. Larger doses are particularly indicated if bacteriophage is employed. It may be that the doses of vaccine and antiviral must vary for individual cases according to the amounts of toxin present, since it is likely that both contain variable amounts of toxin which will vary with different cultures, especially in the cases of streptococci and staphylococci.

When vaccine or antiviral is employed there may be an added advantage in using one of the chemical disinfectants for lavage as suggested in the preceding paper<sup>1</sup> of this series instead of the plain saline solution. Indeed, this would appear to be the better procedure in order to secure the possible benefit of chemical disinfection, especially since the disinfectants and solutions recommended are without injurious effects on the bronchi and phagocytes, but if bacteriophage is employed, the disinfectants should be omitted in the lavage because they may destroy the bacteriophage if the latter is indeed a living virus.

#### SUMMARY

- 1 Phagocytosis is apparently the principal mechanism of defense and recovery in chronic bronchitis, bronchiectasis and other types of suppurative pneumonitis.

- 2 In this connection phagocytosis by cells of the macrophage system with special reference to clasmotocytes would appear to be of special importance.

- 3 Any therapeutic procedure promoting phagocytosis of the streptococci, staphylococci and other organisms in the bronchial secretions of suppurative pneumonitis will likely prove of therapeutic value.

- 4 In this connection is suggested the administration of autogenous vaccines and antiviruses by intrabronchial injection for the purpose of mobilizing phagocytes, stimulating phagocytosis and promoting local and general antibody production.

- 5 Intrabronchial injections of antiviral may also produce direct destruction of infecting organisms in addition to promoting macrophagic phagocytosis and antibody production.

- 6 Intrabronchial injections of bacteriophage may result in the direct destruction of living organisms as well as stimulate phagocytosis.

- 7 Intrabronchial injections of staphylococcus and streptococcus vaccines, antiviruses and bacteriophages have been extremely well borne by rabbits in doses of 1 cc per kilogram of weight every two days for from six to twenty-four injections.

8 Intrabronchial injections of vaccines, antiviruses and bacteriophages, and especially of vaccines and antiviruses, have increased the number of microphages and macrophages in the bronchial secretions of rabbits

9 Intrabronchial injections of vaccines and antiviruses have produced an increase of opsonins and agglutinins in the blood of rabbits

10 Intrabronchial injections of vaccines and antiviruses of type I pneumococcus, hemolytic streptococcus and *Staphylococcus aureus* have increased the resistance of rabbits to intratracheal inoculations of virulent cultures, especially in the case of type I pneumococcus

11 On the basis of these results, it is suggested that the treatment of chronic bronchitis, bronchiectasis and other types of suppurative pneumonitis by bronchial lavage and intrabronchial injections of autogenous vaccines, antiviruses and bacteriophages is worthy of clinical trial

12 Methods are suggested for the preparation of vaccine and antiviruses and their administration by intrabronchial injection alone or in combination with bronchial lavage with chemical disinfectants



# EXPERIMENTAL EDEMA IN NEPHRECTOMIZED DOGS

## III SERUM PROTEINS AND EFFUSION FLUIDS

C J FARMER, M A

F S BARRY, M S, M B

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AND

A C IVY, M D

CHICAGO

Lyon, Shafton and Ivy<sup>1</sup> found that subcutaneous administration of Ringer's solution prolonged the life of bilaterally nephrectomized dogs, and produced a general anasarca, frequently with ascites, hydrothorax and hydropericardium. Barry and Ivy<sup>2</sup> studied the mechanism of the edema and found that edema does not result until water with excessive sodium chloride is supplied, and that retention of urinary products *per se* in the presence of hypochloremia is not conducive to edema even when adequate water is supplied in the form of 4 per cent dextrose solution.

The objects of the present study were first, to observe the changes in serum proteins, and second, to determine the protein content of effusion fluids with the hope that the results might throw further light on the mechanism and type of the edema, and establish some correlation between this experimental edema and some form of clinical edema.

## METHODS

Only large, well nourished dogs of about 20 Kg body weight were employed as experimental animals. The kidneys were removed with strict aseptic precautions and with practically no loss of blood. Beginning on the day after the operation, the dogs were aseptically inoculated subcutaneously with from 1,500 to 2,000 cc of Ringer's solution per day in 500 or 750 cc doses, the amount varying with the weight of the dog (about 90 cc per kilogram). The dogs were allowed water *ad libitum* and were fed as long as they would eat a diet of bread, yellow corn meal and bone soup. Blood samples were taken daily for chemical studies,

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1 Lyon, E E, Shafton, A L, and Ivy, A C. Prolongation of the Life of Nephrectomized Dogs with the Production of Edema, *Arch Int Med* **44** 424 (Sept) 1929

2 Barry, F S, Shafton, A L, and Ivy, A C. Experimental Edema in Nephrectomized Dogs. II The Rôle of Water and Chloride, *Arch Int Med* **51** 200 (Feb) 1933

and the time of occurrence of visible edema was closely noted. The effusion fluid was collected either immediately after death or within two hours. Other pathologic changes were noted at postmortem examination. Occasionally, the pericardial and ascitic fluid was blood-tinged, even though no bleeding point could be found.

Robertson's microrefractometric method<sup>3</sup> was employed to determine the concentration of serum proteins. Although this method had been used previously by Rowe,<sup>4</sup> in a study of protein partition in nephritic serum, and found satisfactory, it seemed desirable to check our values against those obtained on the same serum using chemical methods. For this purpose, serum globulin was precipitated by a 22.2 per cent sodium sulphate solution at 37 C., as suggested by Howe,<sup>5</sup> and the method of Koch and McMeekin<sup>6</sup> was used to determine total nonprotein nitrogen and protein nitrogen in the filtrates and diluted serum. From these values the protein partition was calculated. The quantities estimated by both methods are in general agreement, with the exception of the amount on the seventh day for dog 6. We have no explanation for this single discrepancy, as both sets of determinations were repeated with satisfactory checks. From these results, we feel that conclusions based on values reported in this paper are independent of the method of analysis.

#### EXPERIMENTAL DATA

The material for this series of experiments consisted of thirteen bilaterally nephrectomized dogs, three untreated controls and ten receiving daily subcutaneous injections of Ringer's solution. Two of the controls and three treated dogs were rejected on account of distemper. One treated dog showed blood in the ascitic fluid at autopsy. This was found to be due to the failure of the peritoneum to heal at the site of the wound. The dog was thereupon rejected.

Chart 1 *A* is a graphic indication of the day-to-day serum protein partition of a typical treated dog (dog 6). It will be noted that there is a marked decrease in total serum protein. The albumin fraction falls rapidly, while the globulin after an initial drop shows a marked increase. Reversal of the albumin and globulin fractions occurred in all cases on the fourth or fifth day after operation. Edema developed in four of six animals on the day previous to that on which the albumin-globulin reversal occurred. The concentration of nonprotein substances increased in all cases, but to a less degree than in the untreated control. The small curve in chart 1 *B* is reproduced from the paper of Barker and Kirk.<sup>7</sup> Using plasmapheresis, they noted an increase in globulin as the albumin fraction was lowered. Edema (of the nephrosis type) in their

3 Robertson. *J Biol Chem* **22** 233, 1915

4 Rowe, A. H. *Refractometric Studies of Serum Proteins in Nephritis, Cardiac Decompensation, Diabetes, Anemia, and Other Chronic Diseases*, *Arch Int Med* **19** 354 (March) 1917

5 Howe. *J Biol Chem* **49** 109, 1921

6 Koch and McMeekin. *J Am Chem Soc* **46** 2066, 1924

7 Barker, M. H., and Kirk, E. J. *Experimental Edema (Nephrosis) in Dogs in Relation to Edema of Renal Origin in Patients*, *Arch Int Med* **45** 319 (March) 1930

dogs appeared when the serum albumin reached a value of approximately 0.8 per cent. As will be seen from this and later charts, edema developed in our animals at a higher albumin concentration. Furthermore, we found no relationship between the percentage of serum albumin and the appearance of edema.

The maintenance of normal plasma chlorides during the investigation is shown in table 1. A few comments as to the physical condition of the dog during the experiment are included.

The data from which the graph for dog 6 (chart 1) was constructed are shown in table 2. We include the data on dog 6 because they are

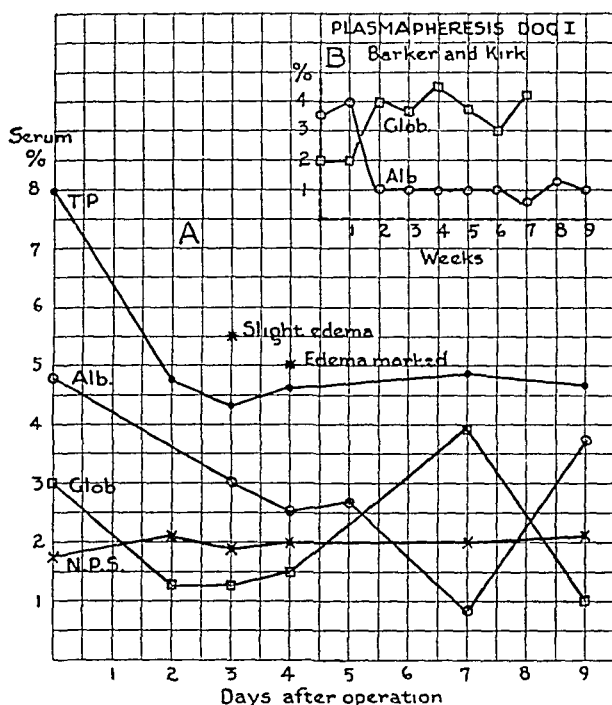


Chart 1—A, day-by-day serum protein partition in dog 6. Note that the albumin-globulin ratio may be reversed in the presence of edema. In charts 1 and 2, *TP* = total serum protein, *Alb* = albumin, *Glob* = globulin, and *NPS* = nonprotein substances. B, plasmapheresis in a dog (from Barker and Kirk<sup>7</sup>).

typical and the animal lived the longest. The lower part of the table presents data obtained on analysis of the effusion fluids. It is important to note the high protein content of all fluids. Additional data on effusion fluids are given in table 4.

Table 3 presents data relative to serum protein levels at the onset of edema. It will be noted that edema appeared in three of six dogs on the fourth day after operation. These animals showed the highest serum albumin percentages of the group, and in each case the albumin concentration was greater than that of globulin. The albumin-globulin

TABLE 1—*Saline Solution Therapy and Blood Chlorides (Dog 6)*

Date	Ringer's Solution Injected, Cc	Blood Chlorides, Mg per 100 Cc	Comment
2/ 3/30	0	482.9	Prior to operation
2/ 4/30	1,500	445.7	
2/ 5/30	1,500	492.3	Slight vomiting
2/ 6/30	1,750		Slight edema in forelegs, vomiting
2/ 7/30	1,750	487.6	Marked edema in all legs, vomiting
2/ 8/30	2,000	490.0	Marked edema, including belly and sero- tum, slight diarrhea and vomiting
2/ 9/30	2,000	514.7	Edema extended to face, severe vomit- ing, slight diarrhea
2/10/30	1,750	510.7	Marked edema of face, severe vomiting, salivation, slight diarrhea, formed stools
2/11/30	1,750	511.2	Marked general edema, extending to lips and tongue, vomiting, formed stools, noticeable weakness
2/12/30	1,750	504.6	Marked general edema, extending to back of head and base of ears, profuse vom- iting, slight diarrhea, marked weakness and difficulty in standing
2/13/30			Died in early morning, no pneumonia, wet lungs, general anasarca

TABLE 2—*Analysis of Blood and of Effusion Fluids (Dog 6)*

Date	Nonprotein Substances, per Cent	Total Proteins, per Cent	Albumin, per Cent	Globulin, per Cent
Venous Blood				
2/ 3/30 (preoperative)	1.93	7.81	4.77	3.04
2/ 5/30	2.12	4.81	3.48	1.33
2/ 6/30	1.88	4.40	3.06	1.34
2/ 7/30	1.98	4.58	3.12	1.46
2/10/30	1.98	4.74	0.78	3.96
2/12/30	2.11	4.64	3.64	1.03
Effusion Fluids				
2/13/30				
Ascitic fluid (1,800 cc clear straw color)	2.17	1.487	0.837	0.650
Pericardial fluid (15 cc clear yellow)	2.45	1.296	1.130	0.166
Pleural fluid (slightly reddish color, right cavity, 35 cc, left cavity, 40 cc)	2.17	1.257	0.973	0.284

TABLE 3—*Serum Protein Level at Onset of Edema*

Dog	Days after Operation	Nonprotein Substances, per Cent	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent
1	4	2.51	6.13	3.29	2.84
2	3	2.08	4.39	2.62	1.77
3	4	2.56	5.52	4.24	1.28
4	5	2.46	4.53	2.02	2.51
6	4	1.98	4.58	3.12	1.46
7	6	2.16	4.85	1.82	3.03

reversal was noted in dog 1 on the day following the onset of edema. In dog 6, blood drawn the third day following the onset of edema showed extreme reversal (globulin, 3.96 mg per hundred cubic centimeters, and albumin, 0.78 mg). Our data on dog 3 indicate that had the animal lived (it lived about six days) reversal would have occurred before the second day following the appearance of edema. In dog 2 edema developed, with the proportion of albumin higher than that of globulin. Serum analyzed on the following day showed approximately equal concentrations of each constituent. The animal died (after five days) before another sample of blood could be obtained. In dogs 4 and 7

TABLE 4—*Analysis of Effusion Fluids and Heart Blood*

Dog	Type of Fluid	Nonprotein Substance, per Cent	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent
2	Ascitic	3.86	3.245	2.000	1.245
	Pericardial	2.51	2.437	0.847	1.590
	Last blood before death	2.26	4.220	2.14	2.080
3	Ascitic	3.29		3.53	
	Pericardial	3.29		3.28	
	Heart blood	3.15	5.484	5.34	0.144
	Last blood before death	2.88	5.230	2.88	2.350
4	Ascitic	2.70		1.65	
	Pericardial	2.75		1.85	
	Heart blood	2.99	4.380	4.23	0.157
	Blood one hour before death	2.85		5.54	
6	Ascitic	2.17	1.487	0.837	0.650
	Pericardial	2.45	1.296	1.130	0.166
	Pleural	2.17	1.257	0.973	0.284
	Last blood before death	2.11	4.640	3.540	1.030
7	Ascitic	2.74			
	Pericardial	2.90	1.866	0.406	1.460
	Heart blood	2.95	4.520	2.080	2.440
	Last blood before death	2.85	4.630	2.010	2.620

edema developed on the fifth and sixth days respectively after operation. In both cases the serum globulin was higher than the albumin. Dog 4 survived for more than two days, and dog 7 for more than three days after the appearance of edema. Since edema developed in dog 6 before the albumin-globulin reversal occurred, and the animal survived for over five days, it is impossible from the present data to draw conclusions suggesting a relationship between serum albumin and serum globulin values at the appearance of edema and during survival periods. There is probably no such relation.

Table 4 presents data on the composition of the effusion fluids, for comparison, figures representing the values of the various constituents in venous blood drawn from one to twenty-four hours prior to death are included. In three cases serum was obtained from heart blood drawn at autopsy (shortly after death). The uniformly high concentration of non-

protein substances in all effusion fluids is striking. In one instance the values are greater than those recorded for the serum of the last blood obtained before death. The concentration of total protein in the various effusion fluids, although high in all cases, is lower than that of blood serum. Of the effusion fluids the protein content is highest in the ascitic, with that of the pericardial and pleural fluids decreasing in the order named. These observations are in agreement with those reported by Loeb, Atchley and Palmer,<sup>8</sup> who studied in patients the equilibrium between blood serum and serous cavity fluids. It is seen, furthermore, that the proportion of albumin to globulin in effusion fluids bears a general relationship to their partition in blood serum. Dogs 6 and 7 illustrate this. From the analytic data available, it is seen that the percentages of albumin and globulin in effusion fluids of dogs 2 and 3 were greater than in dogs 6 and 7. The survival period after the appearance of edema in dogs 2 and 3 was less than two days, while dogs 6 and 7 lived between five and six, and between three and four, days respectively. Dog 4 survived about three days after edema developed and showed an albumin content intermediary between the values of the aforementioned groups.

Chart 2 presents data on an untreated control animal (dog 13) and on a dog in which distemper developed during treatment. Note in dog 13 (graph A) early reversal of serum albumin and globulin curves. The globulin rose to 5.5 per cent on the fourth day after operation, a value much higher than that attained by any treated dog in the series. The albumin dropped rapidly for three days, and then before death increased sufficiently in concentration to elevate the total protein to a high figure. Nonprotein substances increased more rapidly than in treated dogs. Notwithstanding this change in the blood protein picture, edema failed to develop.

In the graph for dog 10 (chart 2B), it will be seen that the amount of serum globulin was greater than that of albumin at the day of operation. This reversal occurred before any clinical manifestation of distemper appeared. Distemper was observed on the day after the operation. This dog received subcutaneous injections of Ringer's solution daily, but it died of distemper, and edema failed to develop. In this case, the daily injection of saline solution could not prolong life sufficiently for edema to develop.

In a second group of five experiments the nephrectomized dogs received injections of a mixture of two-thirds 4 per cent dextrose and one-third Ringer's solution, which was known<sup>2</sup> to prolong life but not

<sup>8</sup> Loeb, Atchley and Palmer. *J. Gen. Physiol.* 4: 591, 1922.

to produce visible edema. Edema did not develop in these dogs. The nonprotein nitrogen in the serum was increased, the total serum protein was decreased, and the albumin-globulin ratio was reversed. Work by Miss Reed and Professor Farmer to be published in detail later shows that the blood potassium, sodium and calcium values remain constant. The phosphorus is increased. In control nephrectomized dogs the amounts of sodium, potassium and calcium in the blood are slightly increased, owing to concentration of the blood. Phosphorus is markedly increased. Table 5 shows the results of a typical analysis of the blood.

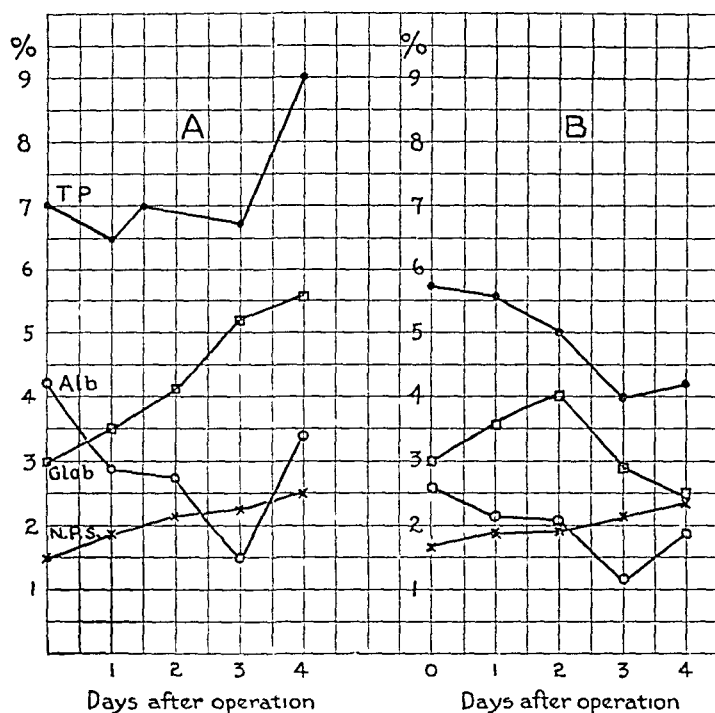


Chart 2—A, data on an untreated control dog (dog 13) B, data on a dog (dog 10) treated with Ringer's solution, in which distemper resulted on the day following the operation

TABLE 5—Chemistry of Blood Serum

Days After Operation	Nonprotein Substances, per Cent	Total Protein, per Cent	Sodium, Mg per 100 Cc	Potassium, Mg per 100 Cc	Calcium, Mg per 100 Cc	Phosphorus, Mg per 100 Cc	Chloride, Mg Sodium Chloride per 100 Cc
Dog 11 (Injected Dextrose 2/3 plus Ringer's Solution 1/3, no edema produced)							
0	1.25	6.30	346.83		13.04		483.2
2	2.21	5.78	344.33	21.0		7.89	
3	2.36	5.50			11.34	6.41	492.3
4	1.82	5.06	313.33	29.5	13.23	7.65	
6	1.93	4.92	306.50	30.0	13.23	11.03	487.6
7	1.98	4.07	305.17	30.5		11.36	
8	2.14	4.07	281.84	31.5	12.29	15.00	504.5
Dog 16 (Untreated Control)							
0	1.25	7.36	308.83	22.0	14.45	1.55	
1	1.64	6.87	347.50	25.0	16.50	2.50	
2	2.57	6.68	351.83	32.0	15.80	2.90	
3	2.57	6.48		33.0	16.10	3.85	
4	2.21	7.01	365.00	32.0		4.70	
5	2.31	7.41	350.83	33.0	19.75	5.20	

## COMMENT

Leiter<sup>9</sup> and Barker and Kirk<sup>7</sup> have produced edema in dogs by inducing hypoproteinemia by the method of plasmapheresis. They were stimulated to perform such experiments by the consistent occurrence of a low plasma protein level in patients with renal edema who were excreting albumin in the urine. Leiter reported that when the plasma proteins had fallen to 3 per cent or less in his dogs, edema occurred. The effusion fluid in Leiter's dogs had a protein content of less than 0.25 per cent and often below 0.1 per cent. Barker reported that "it was impossible to foretell the time of appearance and amount of edema by the total protein level" and expressed the belief that an unusually low albumin content of 0.8 Gm per hundred cubic centimeters was more indicative of the "edema level." He found, further, that a low protein content caused pathologic changes in the renal parenchyma. There was no increase in the blood nonprotein nitrogen in his dogs. The picture presented by Barker's dogs along with the low protein content of the effusion fluid found by Leiter suggests that the edema they produced was comparable to the edema that occurs in "nephrosis" which is sometimes included under the term "chronic parenchymatous nephritis."<sup>10</sup>

The experimental conditions and findings in our dogs are quite different from those of Leiter and Barker. Any change that occurred in our dogs was certainly extrarenal, since the kidneys had been removed. Any change that occurred was due to absolute acute renal insufficiency. We administered water, which in itself does not cause edema, and sufficient chlorides in a "physiologic ratio" to keep the blood chlorides normal, and edema resulted. However, chlorides (most probably sodium chloride) must be administered in excess of the requirements of the body, since edema does not develop in dogs given a mixture of dextrose and Ringer's solution. Our dogs showed a high grade urinary retention with changes in the blood serum protein and a decrease in total protein. The protein content of the effusion fluid was high, which probably denotes an increased capillary permeability, since the protein content of normal peritoneal fluid, according to Vogt,<sup>11</sup> is rarely above 0.7 per cent. These findings are comparable to those in acute glomerular nephritis in man in which there is urinary retention associated with a high protein content (1 per cent) of the effusion fluid according to Beckman,<sup>12</sup> whereas the protein content of the effusion fluid in Leiter's dogs was not more than 0.25 per cent. Our data on the protein content

9 Leiter, L. Proc Soc Exper Biol & Med **26** 173, 1928

10 McLean. Physiol Rev **5** 634, 1925. Loeb, Atchley and Palmer<sup>8</sup>

11 Vogt, E. Arch f Gynäk **120** 40 1923, Med Klin **19** 943, 1923

12 Beckman. Deutsches Arch f klin Med **135** 39, 1921



of the effusion fluid are comparable to those found by Kumpf,<sup>13</sup> who observed edema in two rabbits following repeated hemorrhage, the kidney of one being essentially normal and of the other showing some spontaneous degenerative changes on histologic examination (In this connection the studies of Loeb<sup>14</sup> and Govaerts<sup>15</sup> on peritoneal absorption and on the protein content of the effusion fluid in uranium nephritis are interesting, but not directly apropos) Since our dogs were not losing blood protein through the urine and it was not being removed by us, there are only two possible processes which can have occurred to reduce it, one being that it passed out into the tissue fluids and the other that it was metabolized and not replaced The former is more likely, since we found a high protein content of the effusion fluid, and since starvation has little effect on blood proteins The decrease in blood protein was probably not due to plasma volume, since our hematocrit readings show only a slight increase in plasma volume Whereas plasmapheresis produces edema which may be comparable to that occurring in nephrosis, the type observed in our nephrectomized dogs, we believe, more closely simulates the edema accompanying acute glomerular nephritis in man

The total serum protein was not reduced in untreated nephrectomized dogs, but only in the dogs which received Ringer's solution The reduction in total serum protein in the treated dogs may have played a rôle in the production of edema Whether this is cause or effect cannot be stated from the data The total serum protein fell before visible edema developed That the reduction of total serum protein is not the sole factor in the mechanism of the edema observed in our nephrectomized dogs is shown by the fact that in nephrectomized dogs receiving a mixture of two-thirds 4 per cent dextrose and one-third Ringer's solution, the serum protein decreased, but edema did not result, the water input being the same and the sodium chloride input reduced Even in the low proteinemic edema (plasmapheresis) experiments of Leiter and Barker, sodium chloride was an important factor That low total protein is not the sole factor agrees with the observations of Linder, Lundsgaard and Van Slyke<sup>16</sup> in patients who found serum proteins reduced in the nephrotic type of nephritis, whether or not edema was present They concluded that although a low protein concentration and edema frequently occur together, their relationship is not a simple

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13 Kumpf, A E Experimental Edema and Lipemia Produced by Repeated Bleeding, *Arch Path* **13** 415 (March) 1932

14 Loeb, Leo Edema, Baltimore Williams & Wilkins Company, 1923

15 Govaerts *Bull Acad roy de med de Belgique* **8** 33, 1928

16 Linder, Lundsgaard and Van Slyke *J Exper Med* **39** 887 and 921 1924

one of cause and effect. In our dogs with acute renal insufficiency and lowered serum protein and with water administered to more than compensate for thirst, edema did not develop until salt was added, and the amount of edema was roughly proportional to the amount of salt administered.

Although it logically follows from our observations that restriction of sodium chloride should prevent edema from occurring in acute renal insufficiency, it does not follow that the edema in all patients should be cleared up solely by this restriction, because the mechanism of water balance in some patients may become more or less stabilized, and a nitrogen or protein deficiency may have to be satisfied or the sodium ion replaced by the potassium, calcium or ammonium ion before a normal water balance may be established.

#### CONCLUSIONS

1. Edema developed in four of six animals on the day previous to the albumin-globulin reversal.

2. No relation between the amount of serum albumin and the appearance or presence of edema was evident in treated dogs in which edema developed.

3. Distemper may reverse the albumin-globulin ratio, and the ratio may be reversed in untreated dogs in which edema does not develop and the total serum protein remains fairly constant.

4. Reversal of the serum albumin-globulin ratio has no direct relation to the development of edema.

5. The total serum protein is not reduced in untreated nephrectomized dogs. It is reduced, however, in nephrectomized dogs treated with Ringer's solution. Whether this is a cause or an effect cannot be stated from the data. The total serum protein falls before visible edema occurs. That the reduction in total serum protein is not the sole factor in the mechanism of the edema observed in our dogs is shown by the fact that in nephrectomized dogs receiving a mixture of two-thirds 4 per cent dextrose and one-third Ringer's solution, the serum protein decreased but edema did not result, the water input being the same and the chloride input reduced. We do not doubt that the reduction in total serum protein is a contributory factor, or may be an essential factor, but sodium chloride, or sodium, is certainly an essential factor.

6. The effusion fluids of nephrectomized dogs treated with Ringer's solution have a total protein content ranging from 1.3 to 4 per cent, which is in marked contrast to the effusion fluids in edema produced by repeated plasmapheresis. The greater protein content, we believe, indicates that acute urinary retention increases capillary permeability.

# CARDIOSPASM

WITH A REVIEW OF THE LITERATURE

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In collecting data for teaching purposes regarding mega-esophagus, I was impressed with the lack of any full account of this condition in English Thieding's<sup>1</sup> monograph, the outstanding contribution on this subject to date, published in German in 1921, contains nothing of the work of Plummer and Vinson, not to mention other important American or British writers Beside this, Thieding's paper is given over to an attempt to prove that cardiospasm is a part of autonomic imbalance and that as such it is symptomatic of psychoneurosis It has therefore seemed worth while to connect and publish my notes, using Thieding's paper freely and referring to his large bibliography, exhaustive, doubtless, within the limits of the literature available to that author at that time Data collected from 13 personally observed cases, during five years of existence of the group service of gastro-enterology in the New York University division of Bellevue Hospital, will be given

Cardiospasm has been given different names by different observers, the choice of name depending in most instances on the observer's conception of the cause or the pathology Achalasia of the cardia, simple ectasia of the esophagus, mega-esophagus, preventriculosis, spindle-shaped dilatation of the esophagus and idiopathic dilatation of the esophagus are to be found in use in the literature on the subject

## DEFINITION

Cardiospasm is the common name used for a condition in which, without a demonstrable obstructive pathologic change, and usually without pain, food does not pass readily from the esophagus into the stomach, but is held in the esophagus, which, in the majority of cases, undergoes dilatation, sometimes extreme

## HISTORICAL DATA

Spastic conditions of the esophagus have been recognized since 1733, when F Hoffmann published "*de spasmis gulae inferioris et de nausea*,"

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1 Thieding, F Ueber Cardiospasmus, Atonie und idiopathische Dilatation der Speiserohre, Beitr z klin Chir **121** 237, 1921

but the first case of idiopathic dilatation of the esophagus was described by Purton<sup>2</sup> in 1821, and the second by Hannay<sup>3</sup> in 1833. In 1841, Malrustens<sup>4</sup> described a case of diffuse dilatation of the esophagus without stricture, while Huss reported a similar case a year later. Rokitanski<sup>5</sup> and delle Chiaie<sup>6</sup> both reported cases in 1840, Abercrombie<sup>7</sup> in 1828, Oppolzer<sup>8</sup> in 1851, Spengler<sup>9</sup> in 1853 and Wilks<sup>10</sup> in 1859. In 1876, Zenker and von Ziemssen<sup>11</sup> published a study of this condition, collecting 17 cases from the literature. They emphasized the absence of stenosis and called the condition "simple ectasia." Seventeen cases were thus collected in fifty-five years, and twenty-eight years later, in 1904, von Mikulicz<sup>12</sup> estimated that there were 100 cases in the literature, among which were cases reported by Rumpel, Sievers, Zinnser, Rosenheim, Swain, Lockwood, Meltzer, Gregersen and Johnson. Geppert,<sup>13</sup> in 1914, quoted Neumann's 70 cases reported in 1900, and added 70 more.

By 1896, Wegele, Straus and Lindemann<sup>14</sup> had all investigated cases with various combinations of tubes, copper wires and shot. In 1908, Plummer<sup>15</sup> reported 40 cases from the Mayo Clinic, and in 1912,<sup>16</sup> 156

2 Purton, J. An Extra Ordinary Case of Dilatation of the Esophagus, *M & Physiol J* **46**:540, 1821.

3 Hannay, A. J. An Extraordinary Dilatation (With Hypertrophy) of All the Thoracic Portion of the Esophagus Causing Dysphagia, *Edinburgh M & S J* **40** 65, 1833.

4 Malrustens, quoted by Tyson, Martin and Evans<sup>42</sup>

5 Rokitanski, D. Drei merkwürdige Fälle, spindelförmige Erweiterung der Speiseröhre, *Med Jahrb d k k oesterr Staates* **21**:219, 1840.

6 delle Chiaie, S. Istoria anatomico-teratologica intorno ad una bambina rinocefalo-monocola, Napoli, Tramater, 1840.

7 Abercrombie, John. Pathological and Practical Researches on Diseases of the Stomach, the Intestinal Canal, the Liver, and Other Viscera of the Abdomen, Edinburgh, Waugh & Innes, 1828.

8 von Oppolzer, J. Klinische Vorträge über die Krankheiten der Speiseröhre, Wien *Med* **1** 17, 65 and 177, 1851.

9 Spengler. Beobachtungen einer Hypertrophie der Esophagus, *Wien Med* **3** 385, 1853.

10 Wilks. Lecture on Pathologic Anatomy, London, Longmans [and others], 1859.

11 Zenker, in von Ziemssen. Handbuch der speciellen Pathologie und Therapie, Leipzig, F. C. W. Vogel, 1876, vol. 7, p. 1.

12 von Mikulicz, J. Zur Pathologie und Therapie des Cardiospasmus, *Deutsche med Wchnschr* **30** 17 (Jan 1) 1904, **30** 50 (Jan 7) 1904.

13 Geppert, F. Cardiospasmus und die spindelförmige Erweiterung des Oesophagus, *Centralbl f d Grenzgeb d Med u Chir* **18** 149, 1914.

14 Quoted by Thieding<sup>1</sup>

15 Plummer, H. S. Cardiospasm, *J A M A* **51** 549 (Aug 15) 1908.

16 Plummer, H. S. Diffuse Dilatation of the Esophagus Without Anatomic Stenosis (Cardiospasm), *J A M A* **58** 2013 (June 29) 1912.

cases In 1924, Vinson<sup>17</sup> stated that from 1908 to June, 1923, 415 patients had been treated in the Mayo Clinic No other published series approaches this number

#### PATHOGENESIS

It is natural that early conceptions of this disease should follow the necropsy observations The patient who could not swallow showed at death a thin and dilated sac and no other pathologic change, so that in 1876 Zenker and von Ziemssen<sup>11</sup> called this condition "simple ectasia of the esophagus" In 1882, however, von Mikulicz<sup>18</sup> demonstrated the absence of organic stenosis by means of the esophagoscope and suggested that cardiospasm caused the dilatation This contention was further strengthened by the study of Meltzer<sup>19</sup> published in 1888 It has received wide acceptance, because stretching the cardia produces a symptomatic cure However, this has seemed inadequate to some investigators, and other theories have been suggested Rosenheim<sup>20</sup> expressed the belief that the cause is a primary atony of the musculature of the esophagus Atony of the esophagus after traumatic injury of the vagus, as well as after lead poisoning and infection, has been described by Stephan,<sup>21</sup> von Bergmann<sup>22</sup> and Meyer,<sup>23</sup> who pointed out the susceptibility of the vagus nerve to lead It is a striking fact that no such dilatation of the esophagus is seen in organic stenosis No benign or malignant stricture causes dilatation even approaching the moderate dilatation produced by cardiospasm

Fleiner,<sup>24</sup> Luschka,<sup>25</sup> Zenker,<sup>11</sup> Sievers<sup>26</sup> and others have suggested a congenital tendency in the esophagus to idiopathic dilatation Grein<sup>14</sup>

17 Vinson, P P The Diagnosis and Treatment of Cardiospasm, *J A M A* **82** 859 (March 15) 1924

18 von Mikulicz, J Ueber Gastroskopie und Oesophagoskopie, *Mitth d Ver d Aerzte in Niede-Oest Wien* **8** 41, 1882

19 Meltzer, S G Ein Fall von Dysphagie, *Berl klin Wchnschr* **25** 140, 1888

20 Rosenheim, T Beitrage zur Oesophagoskopie, *Deutsche med Wchnschr* **24** 53 and 75, 1899, Beitrage zur Kenntnis der Divertikel und Ektasien der Speiserohre, *Ztschr f klin Med* **41** 177, 1900

21 Stephan, quoted by Fisher, W, in Henke, F, and Lubarsch, O *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol 4, p 101

22 von Bergmann Ein Fall von Dilatatio oesophagi, idiopathica, *Berl klin Wchnschr* **45** 330 (Feb 10) 1908

23 Meyer, H Entstehung und Behandlung der Speiserohrerweiterungen und des Cardiospasmus, *Mitt a d Grenzgeb d Med u Chir* **34** 484, 1922

24 Fleiner, W (a) *Lehrbuch der Krankheiten der Verdauungsorgane*, Stuttgart, Ferdinand Enke, 1896, (b) *Neue Beitrage zur Pathologie der Speiserohre*, Munchen med Wchnschr **47** 529, 1900

25 Luschka, V H Die spindelformige Erweiterung der Speiserohre, *Virchow's Arch f path Anat* **11** 429 and 473, 1868

26 Sievers, R *Ztschr f klin Med* **49** 45, 1903

reported a case of congenital dilatation, and noted the similarity to Hirschsprung's disease. Early dilatation has been reported by Goppert,<sup>27</sup> Langmead,<sup>28</sup> Cahn,<sup>29</sup> Sternberg<sup>30</sup> and others. Congenital irregularities of the esophagus have been reported extensively (Falkenheim,<sup>31</sup> Stierlin,<sup>32</sup> Wiebrecht<sup>33</sup> and Zusch<sup>34</sup>). Guisez<sup>35</sup> has suggested mechanical irritation of the vagus from poorly masticated food.

Zaaijer<sup>36</sup> expressed the belief that the longitudinal fibers fail in the presence of paralysis of the cardia. Kraus<sup>37</sup> advanced the theory that besides the cardiospasm there must be paralysis of the circular fibers of the esophagus. Martin<sup>38</sup> felt that the dilatation was preceded by esophagitis. Kinking of the esophagus has been suggested.

The lower two thirds of the esophagus is most involved. Lockwood<sup>39</sup> reported a case in which there was a floating right kidney, and he suggested that reflex irritation of the vagus by this or other means may induce the cardiospasm. This possibility is strengthened by the experiments of Openchowsky,<sup>40</sup> and cases with this association have been reported by Smukler<sup>41</sup> and Tyson.<sup>42</sup> Ulcer and cancer of the

27 Goppert, quoted by Lotheissen, G, in Bergmann, E, Bruns, P, and Mikulicz, J. *Handbuch der praktischen Chirurgie*, ed 4, Stuttgart, Ferdinand Enke, 1913, vol 2.

28 Langmead, F. Notes on a Case of Esophagectasis in an Infant, with Radiograms, *Proc Roy Soc Med (Sect Dis Child)* **13**:43, 1920.

29 Cahn, A. Ueber die diagnostische Verwertung der Rontgenstrahlen und den Gebrauch der Quecksilbersonde bei Speiserohrernerkrankungen, *Munchen med Wchnschr* **53** 73, 1906.

30 Sternberg, W. *Munchen med Wchnschr* **62** 1652, 1915.

31 Falkenheim, C. Ein Fall von kongenitaler Cardiastenose mit diffuser Oesophagusektasia, *Mitt a d Grenzgeb d Med u Chir* **33** 113, 1921.

32 Stierlin, R. Ueber diffuse Oesophagusektasie bei wahrscheinlich angeborener Cardiastenose, *Arb a d Geb d Anat path Inst zu Tubingen* **7**:19, 1909.

33 Wiebrecht, K. Ueber die Ectasien des Oesophagus, *Inaug Diss*, Gottingen, W F Kastner, 1897.

34 Zusch, O. Ueber spindelformige Erweiterung der Speiserohre im untersten Abschnitt, *Deutsches Arch f klin Med* **73** 208, 1902.

35 Guisez, J. Spasm of the Esophagus, *Bull Acad de med, Paris* **83** 147 (Feb 17) 1920, *Pathogénie et traitement des grandes dilatations de l'oesophage*, *Presse méd* **29** 661 (Aug 20) 1921.

36 Zaaijer, J H. Cardiospasm in Aged, *Ann Surg* **77** 615 (May) 1923.

37 Kraus. Cardiospasmus, *Sitzungsb d niederrh Gesellsch f natur zu Bonn*, March, 1912, *Deutsche med Wchnschr* **38** 1524, 1912.

38 Martin, E. Zur chirurgischen Behandlung des Cardiospasmus, *Mitt a d Grenzgeb d Med u Chir* **8** 226, 1901.

39 Lockwood, C B. *Brit M J* **1** 1367, 1903.

40 Openchowsky, T. Ueber die gesamten Innervation der Oesophagus, *Deutsche med Wchnschr* **15** 717, 1889, **23** 48, 1897.

41 Smukler, M E. Cardiospasm with Dilatation of the Esophagus, *New York M J* **99** 772 (April 18) 1914.

42 Tyson, J, Martin, E, and Evans, J S, Jr. Diffuse Dilatation of the Esophagus Due to Cardiospasm, *New York M J* **80** 731 (Oct 15) 1904.

esophagus have been reported in connection with cardiospasm, and both diseases have been suggested as excitants from which reflex spasm might occur. In a case of cardiospasm associated with cancer, Loeper and Forestier<sup>43</sup> ascribed the cardiospasm to neurotic lesions found in the vagus and progressive and ascending canceration of the fibers in the region of the cardia. On the other hand, Palugyay<sup>44</sup> has suggested that spasm of the cardia may be compensatory, with pathologic changes below or in case of its own weakness.

Heyrovsky<sup>45</sup> reported degeneration of the vagus and its branches, the trunk showing from partial to complete degeneration. Against this are the reports of Starck<sup>46</sup>, Howship,<sup>47</sup> Rosenheim,<sup>20</sup> Schmidt,<sup>48</sup> Harbitz,<sup>49</sup> and others, who reported no pathologic changes at necropsy. However, Hurst<sup>50</sup> quoted Stokes as having found entire absence of Auerbach's plexus in 2 cases of cardiospasm sent him by Hurst. He gives Rake<sup>51</sup> the credit for first suggesting disease of Auerbach's plexus as a cause of this condition. Mosher and McGregor<sup>52</sup> confirmed the finding of Stokes of inflammation and partial or total destruction of Auerbach's plexus. They quoted Canon as having found that a pressure anemia of a given portion of the intestinal tract produced experimentally was followed in four hours by destruction of Auerbach's plexus and cessation of peristalsis. Cameron<sup>53</sup> reported similar findings in 7 necropsies. In 1, that of a child of 6, acute inflammation of Auerbach's plexus was found. From its character Cameron thought the

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43 Loeper, M, and Forestier, J. Recurring Cardiospasm with Cancer of the Stomach, *Arch d mal d l'app digestif* **11** 307 (Oct.) 1921.

44 Palugyay, J. Compensatory Closure of Esophagus in Dysfunction of the Cardia, *Wien klin Wchnschr* **39** 540 (May 6) 1926.

45 Heyrovsky, H. Casuistik und Therapie der idiopathischen Dilatation der Speiseröhre. Oesophagogaströanastomose, *Arch f klin Chir* **100** 703, 1912-1913.

46 Starck, H. Zur Pathologie der Erweiterungen der Speiseröhre mit besonderer Berücksichtigung des Röntgenverfahrens, *Verhandl d deutsch Kong f inn Med* **29** 122, 1912.

47 Howship, John. Practical Remarks on Indigestion, London, Longman [and others], 1825.

48 Schmidt, M. B. Ueber idiopathische Oesophaguserweiterung, *Deutsche med Wchnschr* **31** 1522, 1905.

49 Harbitz, F. Idiopatisk esophagus-dilatation, *Norsk mag f lægevidensk* **79** 841 (Aug.) 1918.

50 Hurst, A. F. Treatment of Achalasia of the Cardia, *Lancet* **1** 618 (March 19), 667 (March 26) 1927.

51 Rake, G. W. A Case of Annular Muscular Hypertrophy of the Esophagus, *Guy's Hosp Rep* **76** 145 (April) 1926.

52 Mosher, H. P., and McGregor, G. W. A Study of the Lower End of the Esophagus, *Tr Am Laryng Rhin & Otol Soc* **34** 294, 1928.

53 Cameron, J. A. M. Oesophagectasia in a Child, *Arch Dis Childhood* **2** 358 (Dec.) 1927.

neivous lesion not part of an arteriosclerotic process, but "indisputable of bacterial invasion" Vampré<sup>54</sup> reported an epidemic of dysphagia with roentgen signs of cardia and lower esophageal spasm Held and Gross<sup>55</sup> expressed the belief that cardiospasm is primarily the outcome of a hyperirritability of the vagus which may be brought about in the following 5 types of vagotonia In the first type belong persons possessed by inheritance of unstable autonomic systems Bed wetters, periodic vomiters and sufferers from urticaria would be the sort that make up this class The second group would include patients with status lymphaticus with an inherent tendency to vegetative nervous instability The third group would include all patients with reflex cases with such excitants as a floating kidney or ulcer or carcinoma of the stomach The fourth group would include such persons as were poisoned by nicotine, uremia, gout or some other poison with a selective action on the vagus The last group would be made up of such patients as had direct esophageal irritation, such as peptic ulcer of the esophagus, esophagitis or scar tissue formation Mehnert<sup>56</sup> has pointed out abnormalities in the position of the aorta and esophagus as a causal factor

That there is no cardiac sphincter at all has been claimed by Retzius and Cruveilhier, Fleiner,<sup>54</sup> Zaaier,<sup>36</sup> Jackson,<sup>57</sup> Mosher and McGregor<sup>52</sup> and others

On the other hand, Schreiber,<sup>58</sup> Thieding<sup>1</sup> and Hurst<sup>50</sup> expressed the belief that the usual anatomic description of a band of circular muscle fibers forming a sphincter at the lower end of the esophagus is correct

Gubaroff<sup>59</sup> pointed out that the oblique entrance of the esophagus into the stomach gives a valvelike action, and Sternberg<sup>60</sup> expressed the opinion that the cardia is always contracted and has to be forced open Abnormal function, then, would occur when the esophagus failed to overcome this obstruction

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54 Vampré, E Epidemic Intermittent Dysphagia, Policlínico (sez med) **31** 279 (May) 1924

55 Held, I W, and Gross, M H Cardiospasm, J A M A **66** 233 (Jan 22) 1916

56 Mehnert, E Ueber die klinische Bedeutung der Oesophagus- und Aortenvariationen, Arch f klin Chir **58**:183, 1899

57 Jackson, C Bronchoscopy and Esophagoscopy, Philadelphia, W B Saunders Company, 1927, p 73

58 Schreiber Ueber den Schluckmechanismus, Berlin, 1914

59 Gubaroff Arch f Anat u Entwicklungsgesch, 1886, p 395

60 Sternberg, W Die Sekretentfernung bei der Oesophagoskopie, Munchen med Wchnschr **62** 468, 1915



In 1906, Sauerbruch and Hacker<sup>61</sup> suggested that the diaphragmatic muscle may cause the obstruction. In 1914, Bassler<sup>62</sup> independently confirmed this view with five dissections and by roentgen studies. This theory has also been supported by Jackson,<sup>63</sup> who spoke of the diaphragmatic pinchcock constituted by the crura, and described special bundles of muscle fibers which pass from the crura to the esophagus. Jackson expressed the belief that there is no sphincter at the cardiac end of the esophagus; he said that the esophagoscope demonstrates the site of so-called cardiospasm at the hiatus, and suggested the name "phrenospasm" for cardiospasm. Joannides also takes this view, and finds that the muscle fibers of the diaphragmatic pillars bear a great resemblance to those of the anal sphincter.

Mosher and McGregor<sup>64</sup> noted a waistlike constriction above the level of the diaphragm and suggested that this may be caused by pressure of the tips of the lungs. Mosher<sup>64</sup> contended that the esophagus passes through a tunnel of liver, and that any prolapse of the liver would offer obstruction. Shortening the round ligament of the liver or suturing the liver to the diaphragm might relieve this pressure.

#### PREDISPOSING FACTORS

Thieding<sup>1</sup> expressed the belief that the person with a psychasthenic taint is predisposed to cardiospasm, and he took for granted a cortical connection with vegetative imbalance.

Imperator<sup>65</sup> expressed the opinion that cardiospasm may represent the defense against fallatio fantasies. Schindler<sup>66</sup> regarded cardiospasm as the reaction of the patient to the necessity of keeping silent before disagreeable superiors, and he expressed the belief that psychotherapy cures the early stage. This is the answer to "children should be seen and not heard." Plummer and Vinson,<sup>67</sup> in a report in 1921 covering 301 cases, stated that in cardiospasm without esophageal dilatation the patients are frequently of psychoneurotic types. Concerning cardiospasm

61 Sauerbruch, F, and Hacker, R. Zur Frage des Cardiaerschlusses der Speiseröhre, *Deutsche med Wchnschr* **32** 1263, 1906.

62 Bassler, A. Cardiospasm. What Is It? What It Seems to Be, *New York State J Med* **14** 9 (Jan) 1914.

63 Jackson, C. The Diaphragmatic Pinchcock in So-Called "Cardiospasm," *Laryngoscope* **32** 139 (Feb) 1922.

64 Mosher, H. P. Liver Tunnel and Cardio-Spasm, *Laryngoscope* **32** 348 (May) 1922.

65 Imperator, C. J. Cardiospasm, *Arch Otolaryng* **11** 178 (Feb) 1930.

66 Schindler, R. Mechanism and Treatment of Cardiospasm, *München med Wchnschr* **73** 1612 (Sept 24) 1926.

67 Plummer, H. S., and Vinson, P. P. Cardiospasm, *M Clin North America* **5** 355 (Sept) 1921.

with dilatation they believe that, "Contrary to the general belief, cardiospasm is not a psychoneurosis, and patients suffering from it are usually calm and well balanced, with normal nervous systems" Later series, which included Plummer's cases, revealed that in 91 cases of diffuse esophageal dilatation, only 5 patients were neurotic, while in 24 cases of mild cardiospasm without esophageal dilatation, all were neurotic and some hysterical

Straus<sup>68</sup> pointed out that cardiospasm occurs in an asthenic habitus He considered it an atonic process, such as a postural defect of the stomach or the colon

Trauma is thought to be a factor, and this is discussed by Thieding Instances of various kinds of violence followed by cardiospasm are cited It has been suggested that a physical shaking up can injure the ganglion cells of the vegetative plexuses, but Thieding thinks that fear in its various forms furnishes psychic trauma and produces imbalance Sudden anger or fright may precipitate an attack, as pointed out by Fenwick<sup>69</sup>

Endocrine origin of cardiospasm has been suggested However, cardiospasm is not a feature of any of the endocrine entities

An abnormally long esophagus has been suggested by Auerbach<sup>70</sup>

No significant incidence of preceding disease has been established

#### SEX AND AGE INCIDENCE

*Sex* —Esophageal disease is said to be more common in males, and tobacco and alcohol are suggested as possible reasons for this Fenwick<sup>69</sup> found that spasm is common in habitual drunkards, and that a debauch will precipitate an attack Of my 13 patients, none used tobacco or alcohol to excess Neumann<sup>71</sup> found 22 men to 19 women, Geppert's<sup>13</sup> series contained 40 men to 21 women Albu<sup>72</sup> found 20 men to 2 women But Kraus and Ridder<sup>73</sup> found the sexes equally affected In my series, there were 9 women to 4 men

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68 Straus, H Zur Diagnose und Therapie der cardiospastischen Speiserohren-erweiterung, *Berl klin Wchnschr* **41** 1261 (Dec 5) 1904

69 Fenwick, W S Spasmodic Stricture of the Cardiac Orifice of the Stomach, *Brit M J* **1** 1126 (April 30) 1898

70 Auerbach, B Diagnose und Therapie der spindelformigen Dilatationen der Speiserohren, *Therap d Gegenw* **8** 150 (April) 1906

71 Neumann, A Ueber die einfach gleichmassige Erweiterung der Speiserohre, *Centralbl f d Grenzgeb d Med u Chir* **3** 160, 1900

72 Albu, A Ein Fall von hochgradiger Esophagusdilatation, *Berl klin Wchnschr* **45** 1109, 1908

73 Kraus and Ridder Die Erkrankungen der Speiserohre, in Nothnagel *Spezielle Pathologie und Therapie*, Vienna, Alfred Holder, 1902, vol 16, pt 1, p 1

*Age*—In Plummei's series, the average age of onset was 29 years. Cardiospasm may occur at any age. Cases have been reported in infants by Merv,<sup>74</sup> Adams,<sup>75</sup> La Fetra,<sup>76</sup> Beck,<sup>77</sup> Morgan,<sup>78</sup> Lotheissen<sup>79</sup> and others. Table 1 is taken from Thieding.<sup>1</sup>

In 13 cases, the age limit when I first saw the patients varied from 24 to 75. Three patients were 24, 26 and 27, respectively, 2 were 30 and 35, 4 were 43, 45, 48 and 48, and 1 each was 50, 58, 61 and 75. The wide age incidence is little affected by subtracting the duration of the cardiospasm from the onset to the time of admission to the hospital from the patient's age at admission. This leaves from 17 to 72 years as the age of onset, the average age being 38.

TABLE 1—*Age Incidence of Cardiospasm*

Age	Males	Females
Up to 10 years	6	3
10 to 20	20	14
20 to 30	26	18
30 to 40	33	9
40 to 50	16	13
50 to 60	7	1
60 to 70	4	1

#### PATHOLOGY AND FREQUENCY

*Pathology*—The dilatation may be absent early or it may be slight. Cases in which there were 2 or 3 liters have been reported.<sup>21</sup> Measurements of 10.5 cm. for transverse diameter, a circumference of 24 and 30 cm. and lengths of 40 and 46 cm. are quoted by Fisher.<sup>14</sup>

The esophagus is spindle-shaped or club-shaped, with the bowl of the club down. Less often it is sausage-shaped. The dilatation commonly can be shown to stop above the cardia at the diaphragm. The esophagus may be thickened to 9 mm., as has been shown by Starck.<sup>46</sup> This is mostly evidenced by hypertrophy, sometimes partly by inflammation. There is often chronic inflammation with warty, whitish thickening of the mucosa, which may be like leather. In the submucosa there is round cell infiltration. The muscularis may show fatty degenera-

<sup>74</sup> Merv. *Rev. gen. di clin. et de therap.* **22** 51, 1906.

<sup>75</sup> Adams, S. S. A Case of Spasmodic Stricture of the Esophagus, *Arch. Pediat.* **26** 170 (March) 1909.

<sup>76</sup> La Fetra, L. E. Spasmodic Stricture of the Esophagus, *Arch. Pediat.* **26** 754 (Oct.) 1909.

<sup>77</sup> Beck, C. Kardiospasmus im Säuglingsalter, *Monatschr. f. Kinderh.* **9** 555 (Oct.) 1911.

<sup>78</sup> Morgan, W. G. Cardiospasm in Infants, *M. Rec.* **80** 172 (July 22) 1911.

<sup>79</sup> Lotheissen, G., in Bergmann, E., Bruns, P., and Mikulicz, J. *Handbuch der praktischen Chirurgie*, ed. 4, Stuttgart, Ferdinand Enke, 1913, vol. 2.

tion and infiltration. The muscle is often pigmented and may show hyaline changes. There may be atrophy of the wall in all layers. An association of congenital cleft remnants has been pointed out by Dierling<sup>80</sup>. Hypertrophy is likely to prevent a primary atony. If vagus disease is the cause, atony should be the common finding without hypertrophy, instead of the reverse being true. There is usually more or less chronic esophagitis.

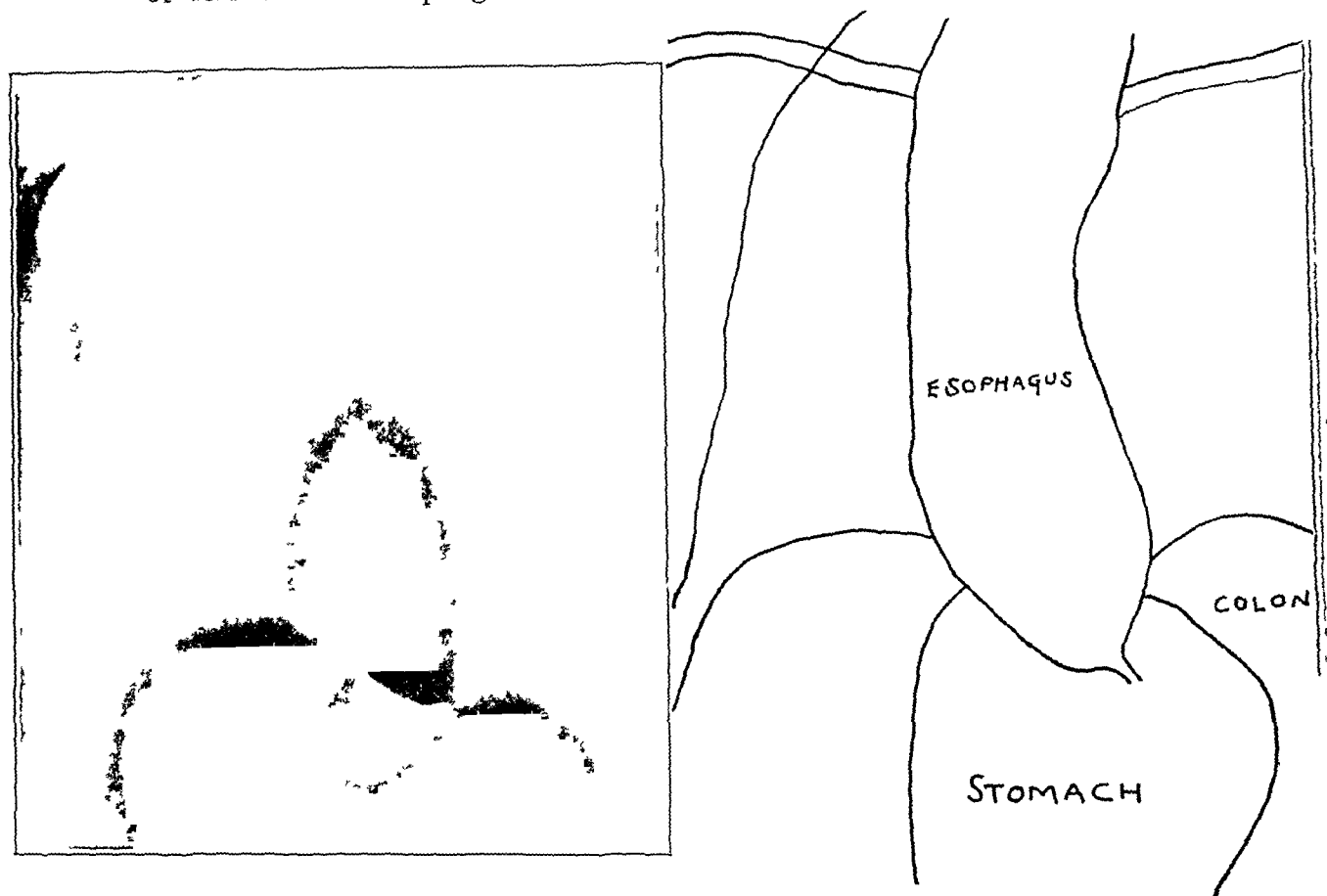


Fig 1—The esophagus is of the club-shaped variety and seems to show obstruction at the cardia and not at the diaphragm.

*Frequency*—Thieding estimated that from 3 to 10 cases of cardiospasm are seen in any hospital in a year. There were 10 cases in Bellevue Hospital in 1930.

#### SYMPTOMS

The symptoms may begin suddenly, as in Tyson's case. Usually they come on gradually, with free intervals. If the onset is sudden, the patient says that while eating he had something stick in his gullet. I have twice been told that the initial symptom was caused by ham that had not been chewed sufficiently. The first attack may be severe. The

<sup>80</sup> Dierling, H. Ueber diffuse Dilatation der Speiserohre, Inaug. Diss., Rostock, Adlers Erben, 1910.

patient is unable to get the offending bolus up or down. He may not be able to swallow water or even saliva. If he is able to swallow water, he may be able to force the solid food into the stomach.

Plummer divides the symptoms of cases with gradual onset, and this includes almost all cases, into three stages. These symptoms depend directly on the pathologic changes. In the first stage the cardia intermittently offers resistance to the passage of food. At all times, however, the esophagus is able to force food through. The patient then complains of discomfort, possibly pain on swallowing and sometimes of choking while eating. A common formula is "My food seems to stick here."

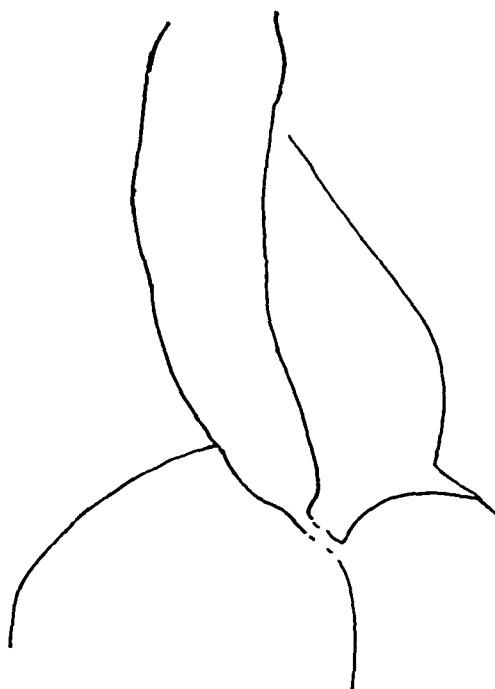
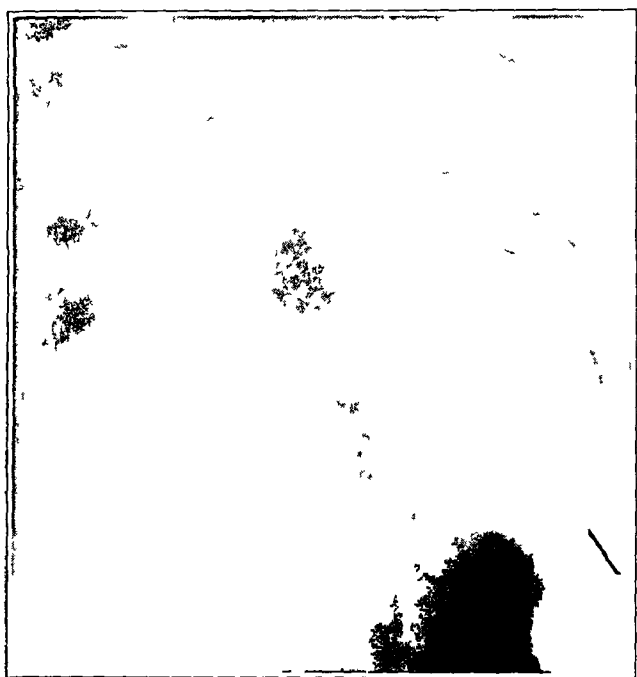


Fig 2—Spindle-shaped dilatation of the esophagus. The obstruction seems to be at the diaphragm.

There is no regurgitation of food in this stage. In the second stage the spasm of the cardia has become so strong that food cannot be forced through readily, and regurgitation takes place during eating. Dilatation behind the spastic cardia follows, which allows the accumulation of food in the dilated esophagus. This leads to the symptoms of the third stage, which are those of regurgitation at irregular intervals. The patient fills his esophagus to its capacity, which may be a pint or more and then may regurgitate a certain amount directly or may regurgitate at irregular intervals. In the second stage the spasm may occur with some meals and be absent with others, so that it has an irregular character, but when it does take place it is during eating. In the third stage the regurgitation is also irregular but takes place at other times than during

actual eating, that is, just after the pouch has been filled or at varying periods afterward. These three stages shade into each other. After esophageal dilatation has taken place the food residuum gives a sensation of weight in the chest. This weight in the chest is said to be increased during anxiety, with cyanosis and cold perspiration. Verbrycke<sup>81</sup> has reported anginal pain with cardiospasm. Patients also complain of pain behind the whole sternum and the ramus of the lower jaw. The food regurgitated is not sour. The patient is unable actually to vomit or belch. The inability to belch is the reason for the anginal attacks, according to Fenwick. Gas gathers in the stomach until the organ is

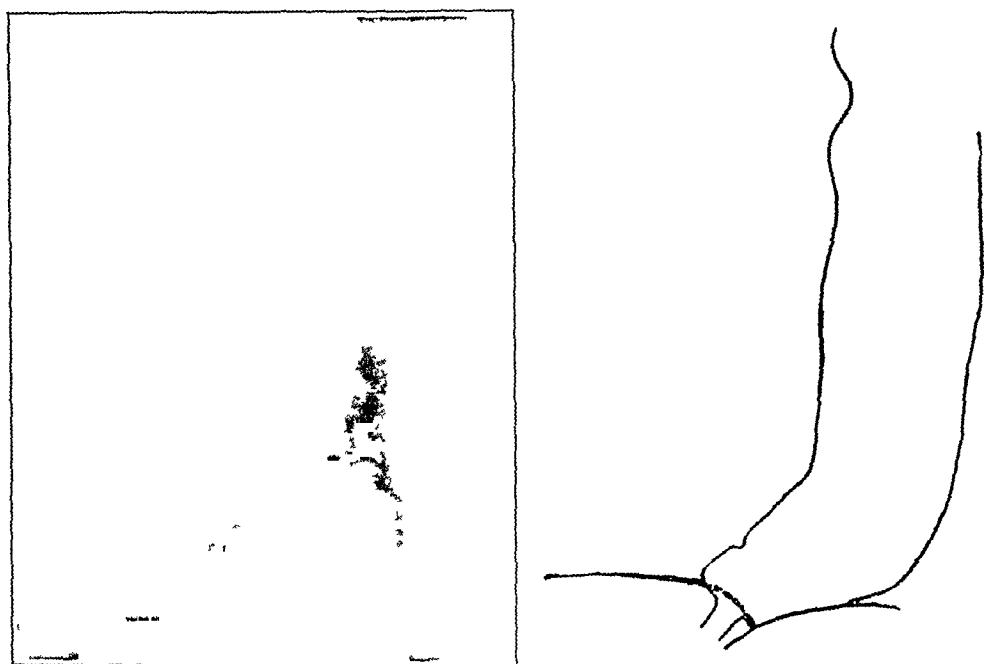


Fig 3—Sausage-shaped dilatation of the esophagus, showing some wavy contour above. The obstruction is at the diaphragm.

distended. Pain, sweating, palpitation and anxiety give the picture of coronary angina. My patient with transient spasm could belch and had acid eructations while asleep, which awakened him.

Rumination has been reported by Luschka<sup>25</sup>

Acetone in the urine is a finding when undermaintenance of nourishment occurs.

The chief complaint is not always dysphagia, and the history may be misleading. Thus, one of my patients complained of knifelike pains over the precordium with morning vomiting, another complained that she had a peculiar pain over the epigastrium. A third said that on attempt-

<sup>81</sup> Verbrycke, J. R., Jr. Cardiospasm, Associated with Aneurysm, Aortitis and Angina, with Report of Twenty-Three Cases, *South M J* **16** 338 (May) 1923.

ing deglutition she began to have a sensation in the throat as if everything tightened, it would then become so constricted that it felt like wood. This was intermittent, and three years later she began to regurgitate. Friedrich's<sup>82</sup> patient, a girl of 10, had attacks of coughing during which she would lie down and which were relieved by vomiting. Bard's<sup>83</sup> 2 patients found that they could swallow better when standing.

It is usually stated that solid foods are retained first, and the patient forces them through. This is accomplished in various ways: by swallowing saliva, by drinking liquids, by breathing, by pressure on the neck, in taking certain postures and by compression of the thorax. It becomes more and more difficult to swallow solid foods. Then soft, pultaceous foods are taken with difficulty, and finally liquids are passed more and more slowly into the stomach. Yet one of my patients with moderate dilatation of the esophagus found that the easiest foods to swallow, for her, were chop suey, corn beef hash, milk toast, macaroni and creamed vegetables. Deep breathing is thought by some to aid swallowing.

It is also said that warm liquids are more easily swallowed than cold, yet my patient who preferred chop suey could swallow ice cold water easier than warm tea or coffee.

Patients complain of vomiting, but if questioned closely or observed it will be discovered that the so-called vomiting is really regurgitation. One of my patients emptied her esophagus every morning and was all right for the day. Sometimes the regurgitation is difficult and accompanied by coughing. At other times the patients, by putting their heads low, can evacuate their gullets with comparative ease. In my case that terminated fatally the patient complained of paroxysmal pain over the upper part of the abdomen. Three attempts were made to visualize her gallbladder by the Graham method, without success. At operation the gallbladder and ducts were found to be normal. The paroxysmal pain was not explained unless it was part of the substernal anginoid pain described. Starck<sup>84</sup> expressed the belief that many cases pass for gallstones, coronary angina, neurasthenia and peptic ulcer, and he saw 5 cases in which the patients were operated on for ulcer.

My 12 patients with esophageal dilatation showed no nervous symptoms. One woman, 43 years old, had an uncle who was mentally defective. She thought that the onset of her cardiospasm, thirteen years

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<sup>82</sup> Friedrich, H. Diagnosis of Dilatation of Esophagus, *Munchen med Wchnschr* **71** 1278 (Sept 12) 1924.

<sup>83</sup> Bard, L. Mega-Esophagus, *Arch d mal de l'app digestif* **10** 116 (March) 1919.

<sup>84</sup> Starck, H. Die Behandlung der Dilatationen und Divertikel der Speiserohre, *Deutsche med Wchnschr* **39** 2496 1914. *Munchen med Wchnschr* **71** 334, 1924.

before, was while she was very nervous. The case of intermittent spasm without dilatation occurred in a man aged 47. His mother possibly had a mild manic-depressive psychosis. He had been a sleep-walker and had a duodenal ulcer, but showed no other neurotic taint.

Rivers and Bueermann<sup>85</sup> reported 3 cases in which attacks of unconsciousness were associated with intermittent cardiospasm, one being a very definite case. They called these attacks, which were short, "epileptiform," and compared them to laryngeal epilepsy. The patient suddenly becomes unconscious while eating. He recovers immediately and goes on eating.

#### PHYSICAL SIGNS

Various physical signs have been described. Dulness to the right of the sternum, below which it changes to tympany when the esophagus is full of air, moist râles when air is pumped in and absence of the second swallowing sound have been described. Bradycardia was described by Heyrovsky,<sup>45</sup> Kaufmann and Kienbock<sup>86</sup> and Schulze.<sup>87</sup> It did not occur in my series.

Hyperacidity is often found in the stomach, but 1 of Soper's<sup>88</sup> patients had achlorhydria. Hyperacidity would be the thing to expect with vagus preponderance, but Thieding pointed out that a vegetative disharmony is rarely pure, and that mixed sympatheticotonia and vago-tonia are described by Eppinger and Hess.

#### ASSOCIATED DISEASES

The association of diverticulum of the esophagus with cardiospasm has been mentioned by Zohlen and Vinson,<sup>89</sup> Fitzgibbon,<sup>90</sup> Bull,<sup>91</sup> Dufour,<sup>92</sup> Van den Wildenberg,<sup>93</sup> Freud<sup>94</sup> and others.

85 Rivers, A. B., and Bueermann, W. H. Recurring Epileptiform Attacks with Symptoms of Spasm at Cardia, *M. Clin. North America* **8** 1341 (Jan.) 1925.

86 Kaufmann, R., and Kienbock, R. Ueber Erkrankungen der Speiseröhre, *Wien klin. Wchnschr.* **22** 1199, 1909.

87 Schulze, J. Röntgenologische Beobachtungen über funktionelle Verhältnisse der Speiseröhre, *München med. Wchnschr.* **64** 879, 1917.

88 Soper, H. W., and Cassidy, L. D. Cardiospasm with Special Reference to Etiology, *Am. J. M. Sc.* **177** 386 (March) 1929.

89 Vinson, P. P. Cardiospasm Associated with Esophageal Diverticula, *New York M. J.* **117** 540 (May 2) 1923.

90 Fitzgibbon, J. H. Cardiospasm and Concomitant Esophageal Diverticulum, *J. A. M. A.* **86** 1614 (May 22) 1926.

91 Bull, P. N. So-Called Idiopathic Dilatation of the Oesophagus, *Ann. Surg.* **81** 59 (Jan.) 1925.

92 Dufour, H. Bull. et mém. Soc. méd. d'hôp. de Paris **19** 1057, 1902.

93 Van den Wildenberg, L. Quelques cas de méga-œsophage, *Ann. de mal. de l'oreille, du larynx* **43** 945, 1924.

94 Freud, J. Zur Röntgendiagnose des seltenen tiefsitzenden Oesophagus-divertikels, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **28** 559, 1921.



Asthma is said to be frequently associated with cardiospasm by Scollery, von Bergmann<sup>95</sup> and Lindvall<sup>96</sup>

Other spastic conditions have also been mentioned Zinn<sup>97</sup> found esophageal spasm behind the heart Thieding found spasm behind the bifurcation I have had a patient with spasm behind the larynx

The association with peptic ulcer is common Heyrovsky, quoted by Soper and Cassidy,<sup>88</sup> reported 6 cases connected with gastric ulcer, and found 7 cases of ulcer in a series of 29 In this connection, the experiments of Gundelfinger<sup>98</sup> relative to a neurogenous vagus preponderance influencing the formation of ulcer is interesting The autonomic origin of ulcer is discussed by von Bergmann,<sup>95</sup> Kaufmann,<sup>99</sup> Muller<sup>100</sup> and Kuntz,<sup>101</sup> among others, and Westphalen<sup>102</sup> has pointed out that disease of the autonomous centers can cause an independent organic neurosis of the cardia and the stomach which may be due to disharmony of the plexus of Openchowsky and that of Auerbach

Carcinoma of the stomach and esophagus is found in significant association It was present 3 times in Soper's<sup>88</sup> series of 29 cases Thieding found that it is a complication 25 times more likely than in the normal esophagus Albu,<sup>72</sup> Bensaude and Guénaux,<sup>103</sup> Guisez,<sup>35</sup> Flemer,<sup>24b</sup> Grund,<sup>104</sup> Knaut,<sup>105</sup> and many others have reported cancer and cardiospasm De Ancaes<sup>106</sup> reported the association of sarcoma

Gallstones are also mentioned in association

95 von Bergmann, G V Das Spasmogene Ulcus pepticum, Munchen med Wchnschr **60** 169, 1913

96 Lindvall, H Case of Diffuse Dilatation of the Esophagus Combined with Bronchial Asthma, Hygiea **77** 860, 1915, Zentralbl f Chir **43** 99 (Feb 5) 1916

97 Zinn Gleichmassige Erweiterung der Speiserohre, Berl klin Wchnschr **47** 1515 (Aug 8) 1910

98 Gundelfinger, E Klinische und experimentelle Untersuchungen uber den Einfluss des Nervensystems bei der Entstehung des runden Magengeschwurs, Mitt a d Grenzgeb d Med u Chir **30** 189 and 229, 1918

99 Kaufmann, R Ueber den Einfluss des Schmerzes und der Digitalis auf die Herzarbeit des normalen Menschen, Ztschr f exper Path u Therap **12** 165, 1913

100 Muller, E F Ueber eine gemeinsame Steuerung von Haut und Lebergebiet, Munchen med Wchnschr **73** 9 (Jan 1) 1926

101 Kuntz, A The Autonomic Nervous System, Philadelphia, Lea & Febiger, 1929

102 Westphalen, H Ein weiterer Fall von diffuser idiopathische Oesophagusdilatation, Arch f Verdauungskr **5** 106, 1899

103 Bensaude, E, and Guénaux, G Rev de med **38** 65 (Feb) 1921

104 Grund, in discussion of Beneke Ueber Oesophagusdilatationen, Munchen med Wchnschr **61** 1882, 1914

105 Knaut, B Ueber die durch Speiserohrenkrebs bedingten Perforationen der benachbarten Blutbahnen, nebst einer Beobachtung von primarer Oesophagusdilatation und von Leukoplakia oesophagi, Inaug Diss, Berlin, Vogt, 1896

106 de Ancaes, C Idiopathic Dilatation of the Esophagus, Lisboa med **2** 415 (Sept) 1925

No associated disease of any significance was found in my series. None of the patients had a positive Wassermann reaction, although one woman had 6 miscarriages in 9 pregnancies, and another had 1 stillbirth in 5 pregnancies, a third had 1 miscarriage and 1 healthy child. The first of these patients had had measles, chicken-pox, pertussis, pneumonia and scarlet fever. The second patient had had rheumatic fever and pneumonia. The third had had influenza. Of the remainder, 1 woman, 30 years old, married but never pregnant, had had measles and mumps. A 75 year old man with cardiospasm of two years' duration had used alcohol in moderation, he gave a history of "blood poisoning" two years before and gonorrhea forty years before. No other history of disease was obtained. The woman, aged 43, who had 6 miscarriages, had had a complete hysterectomy three years before she was seen. Her cardiospasm was of thirteen years' duration. The 75 year old man had had a cyst on his right eye removed six years before.

#### DIAGNOSIS

Various methods of diagnosis have been suggested and used. Before roentgen study was possible, the usual methods were several. Auscultation for the second swallowing sound, which is absent in cardiospasm, was recommended. A device of Meltzer and Rumpel was the double tube test, which consisted in passing a tube into the stomach and another along the side into the esophageal pouch. The acid secretion of the stomach differed from the esophageal contents, so that matter aspirated from the two cavities gave a different appearance and response to tests. In the esophageal contents there are almost always great quantities of thickropy mucus. The size of the dilatation was measured by filling the pouch with water and aspirating.

*Esophagoscopy*—This method of examination is, in proper hands, the ideal method for diagnosis in most diseases of the esophagus. It is perhaps less valuable in mega-esophagus than in any other condition. Unfortunately it is a hazardous procedure in any but skilled hands and should not be attempted by the novice without instruction and supervision. Jackson<sup>57</sup> emphasized that injury to the crico-arytenoid joint, paralysis due to pressure on the recurrent laryngeal nerve, perforation of the esophageal wall and rupture of an aneurysm are possibilities without gentleness, care and experience, he also warned against attempting esophagoscopy in patients with tuberculosis, heart failure or some other advanced organic disease. I have seen 1 death during esophagoscopy without apparent reason. In cases of cardiospasm, esophagoscopy is largely valuable in excluding other diseases particularly cancer.

*Roentgen Study*—This is the accurate method of demonstrating cardiospasm, and by this method diagnosis can be made and complications excluded. Cardiospasm diagnosed during life was a great rarity before roentgen study was possible. Up to 1904, 100 cases were reported. During 1930, there were 20 cases diagnosed in the Department of Hospitals of the City of New York. Carman<sup>107</sup> gave the roentgenologic characteristics as blunt or regularly conical obstruction at or near the cardia, with secondary dilatation of the esophagus above. The smooth symmetrical termination of the shadow is a feature and usually comes at the hiatus and less often at the cardia. Dilatation may reach a point where the contents are a pint or more. Cardiospasm must be differentiated from benign organic stricture and from carcinoma. In differentiation from the latter, it is useful to know that carcinoma rarely produces its obstruction at exactly the hiatus, but usually extends above. In carcinoma there is irregularity of the shadow as it tails out. Benign stricture is usually irregular also, though sometimes a differential diagnosis is difficult.

The esophagus is seen best in the oblique, either in the right or left oblique position of Holzkecht or in the left oblique, and Stierlin<sup>108</sup> suggested the advantage of profile views. In cardiospasm one notes at once the contrast meal retained in the esophagus, with or without a demonstrable small stream trickling into the stomach. The striking thing is the size of the esophagus, which may be large. The lower end is cone-shaped, and the tip points to the left below the dome of the diaphragm. The length of the esophagus may be increased, so that it presents a wavy appearance. It may be cylindric and of uniform width, it may be spindle-shaped, with the dilatation in the center, or it may have a champagne bottle shape.<sup>1</sup> In 1914, Lambert<sup>109</sup> described the 3 contours as fusiform, flask-shaped and S-shaped. Fleiner<sup>21b</sup> has called attention to the hen beak appearance of the shadow that projects into the stomach, which he thinks is due to the gastric pathway. Hirsch<sup>110</sup> expressed the belief that this is due to the stream passing into the longitudinal rugae. Einhorn and Scholz<sup>111</sup> have made use of a delineator string which is swallowed and gives the esophageal course.

107 Carman, R. D. *The Roentgen Diagnosis of Diseases of the Alimentary Canal*, Philadelphia, W. B. Saunders Company, 1921.

108 Stierlin, R. *Klinische Röntgendiagnostik des Verdauungskanales*. Munich, J. F. Bergmann, 1916.

109 Lambert, A. V. S. *Treatment of Diffuse Dilatation of the Oesophagus by Operation. Report of a Case*, Surg., Gynec. & Obst. **18** 1, 1914.

110 Hirsch, A. *Ueber diffuse Dilatation des Oesophagus durch Cardiospasmus*, München med. Wchnschr. **40** 1149, 1919.

111 Einhorn, Moses, and Scholz, T. *X-Ray Findings with the Delineator in Cardiospasm*, Med. Rec. **96** 715, 1919.

Iglauer<sup>112</sup> recommended the use of pneumoperitoneum in the roentgen study of cardiospasm. In one case, he found that this showed adhesions between the diaphragm and the liver, encroaching on the abdominal esophagus.

#### COMPLICATIONS

The complications of cardiospasm which are dependent on it are rupture of the cardiospasm with mediastinitis, either spontaneous or by bougie, ulcer of the esophagus or stomach, which must be considered in mechanical treatment, and carcinoma of the esophagus. Thomas and Jewett<sup>113</sup> reported a case of pneumonia following aspiration of fats from a dilated esophagus due to cardiospasm.

#### PROGNOSIS

When treated by mechanical dilatation, the patients recover. Treatment is easier the earlier it is done. There is some mortality with the

TABLE 2—*Duration of Cardiospasm*

Duration	Cases
1 year or less	23
Less than 5 years, over 1	59
Less than 10 years, over 5	33
Less than 15 years, over 10	17
Less than 20 years, over 15	9
Less than 30 years, over 20	7
Over 30 years	1

procedure. Perforation of a paper thin esophagus is possible. It is fortunate that hypertrophy is the rule. Rupture of the cardia or injury to an ulcer just above, in or below the cardia may result in hemorrhage or perforation. So, as a matter of prognosis, the accidents of treatment constitute the chief hazard, although Zweig<sup>114</sup> reported a case of Wicks', with fatal hemorrhage from an ulcer in the dilated portion.

Untreated patients may live for years on a diet so modified that enough food gets into the stomach to support life. The obstruction may reach such a degree as to cause death by starvation.

The duration of cardiospasm from the beginning to the time of observation is given by Thieding in table 2.

112 Iglauer, S. Pneumoperitoneum as an Aid in the Diagnosis of Cardiospasm, *New York M J* **115** 745 (June 21) 1922.

113 Thomas, W. S., and Jewett, C. H. Pneumonia Following the Aspiration of Fats from the Esophagus Dilated as a Result of Cardiospasm, *Clifton M Bull* **12** 130 (Dec.) 1926.

114 Zweig, W. Ueber Kardiospasmus, *Wien klin Wchnschr* **22** 740, 1909.

My 13 cases were of ten months, one, two, three, three, three, five, five, six, six, seven, ten and thirteen years' duration Snodgrass<sup>115</sup> reported a case of fifty-two years' duration

#### TREATMENT

Medical treatment with atropine has proved disappointing Papaverine has been used and was believed by Thieding to cure one of his patients However, Boehm<sup>116</sup> found no benefit from papaverine, and Assmann found no effect with this drug in 3 cases Boehm found that after the administration of pilocarpine there was shortening of the esophagus with overflow Epinephrine relaxed the cardia but the effect was transitory No other drugs produced favorable therapeutic results

In 1900, von Mikulicz<sup>12</sup> performed gastrostomy on a gull to dilate the cardia Three years later he opened the stomach of another subject and, having stretched the cardia with 3 fingers, he introduced a rubber-covered dilator and further stretched the cardia to a circumference of 13 cm He performed this operation 6 times with good results Ledderhose<sup>14</sup> in 1904, Wilms<sup>14</sup> in 1904 and Goldmann<sup>14</sup> in 1905 reported single operations In 1906, Erdmann,<sup>117</sup> of New York, operated on a patient of Lockwood's, with recovery In 1910, Wendel<sup>118</sup> performed the first cardioplasty Watts<sup>119</sup> expressed the belief that cardiospasm is likely to recur after dilatation and after the Mikulicz operation He had a patient who was only temporarily improved by the Mikulicz operation on whom he did what he believed was the second cardioplasty after the manner of Wendel Heller<sup>120</sup> made two longitudinal incisions, one anterior and one posterior In the Wendel and Watts operations, one incision only was made, the longitudinal The beginnings and ends of the incisions were then approximated, the sides were thus bent on themselves and the upper half was sutured to the lower half De Brune, Groeneveldt and Zaaijer<sup>36</sup> reported success with a single anterior incision Heyrovsky<sup>45</sup> loosened the cardia at the hiatus and anastomosed the esophagus and stomach Haggstrom<sup>121</sup> collected 29

115 Snodgrass, T J Case of Cardiospasm with Enormous Dilatation of the Esophagus, *J Iowa M Soc* **11** 212 (June) 1921

116 Boehm, G Der Cardiospasmus mit Ektasie der Speiserohre und seine Behandlung, *Deutsches Arch f klin Med* **136** 358 (July 5) 1921

117 Erdmann, J F Cardio-Spasm, *Ann Surg* **43** 224 (Feb) 1906

118 Wendel Zur Chirurgie des Oesophagus, *Arch f klin Chir* **93** 311, 1910

119 Watts, S H Cardioplasty for Cardiospasm, *Ann Surg* **78** 164 (Aug) 1923

120 Heller Extramukose Cardioplastik beim chronischen Cardiospasmus mit Dilatation des Oesophagus, *Mitt a d Grenzgeb d Med u Chir* **27** 141, 1914

121 Haggstrom, P Heyrovsky's Operation for Cardiospasm and Dilatation of the Esophagus, *Acta chir Scandinav* **66** 345 1930

cases in which Heyrovsky's operation was performed by the transpleural route. These, he stated, were all successful, whereas 2 of every 5 patients die when the transpleural route advocated by Sauerbruch<sup>122</sup> is used.

Freeman<sup>123</sup> pulled up the esophagus and, turning the slack portion in, made an intussusception, with apparent cure twenty years later. Pamperl collected the cases of 14 patients operated on by the Mikulicz method, with 12 cured and 2 improved. Walton has operated on 14 patients with satisfactory results. Crone-Munzebrock,<sup>124</sup> Greenwood and others have also endorsed this treatment.

Following the success of the Mikulicz operation, various efforts were made to dilate the cardia by expanding instruments introduced into the cardia through the mouth. If such an instrument could be devised, it seemed reasonable that abdominal section could be done away with except in unusual and infrequent cases.

Rosenheim,<sup>20</sup> Lockwood,<sup>39</sup> Einhorn,<sup>125</sup> Gottstein<sup>126</sup> and others devised instruments for this purpose. Gottstein's sound is generally given priority in the German literature, but it was in 1898 that Russell<sup>127</sup> reported that in a radius of less than 40 miles from Southport, England, he had seen 7 cases of a form of stricture of the esophagus which he believed could not be extremely rare. Russell reported good results from stretching the stricture by an expanding dilator to a caliber approaching that of the normal esophagus. This was done with bags of increasing size at several sittings. He made sausage-shaped silk bags which were made air tight by a thin rubber bag within and mounted on the end of a hollow tube. This was passed through the stricture collapsed, and was blown up with an air syringe when in position. By gradual dilatation, Russell cured 4 of 6 patients and improved another very much. The seventh patient he did not treat.

122 Sauerbruch, F. Oesophagusstriktur, Cardiospasmus, Verhandl d deutsch Gesellsch f Chir **45** 149, 1921.

123 Freeman, L. Operation for Relief of Cardiospasm Associated with Dilatation and Tortuosity of Esophagus, Ann Surg **78** 173 (Aug) 1923.

124 Crone-Munzebrock, E. Operative Treatment of True Cardiospasm, Zentralbl f Chir **53** 2386 (Sept 18) 1926.

125 Einhorn, Max. Report of a Case of Idiopathic Dilatation of the Esophagus with Description of a New Cardio Dilator, New York M J **89** 1077 (May 29) 1909, Additional Remarks on Cardiospasm and Idiopathic Dilatation of the Esophagus, M Rec **83** 369, 1913.

126 Gottstein, G. Die operative Behandlung Cardiospasmus, Zentralbl f Chir **31** 1362 (Nov 26) 1904, Weitere Fortschritte in der Therapie des chronischen Cardiospasmus, Arch f klin Chir **27** 497, 1908.

127 Russell, J C. Diagnosis and Treatment of Spasmodic Stricture of the Esophagus, Brit M J **1** 1450 (June 4) 1898.

One patient he did not help Sippy<sup>128</sup> was able to confirm these results in 1906 Plummer<sup>129</sup> made use of a similar method, employing water instead of air to dilate the rubber bag In 1908, he had treated 40 patients by this method This number he had increased to 156 by 1912, and in 1923 Vinson had increased this series to 415

Ordinary bougie treatment may help symptoms partially and temporarily, but dilatation must be carried further for permanent and striking results Oehler<sup>130</sup> reported good results from passing the stomach tube He teaches his patients to pass it and when passage is effected without discomfort, the patient is usually cured

Several different forms of dilating instruments are in use The simplest of these consists of an ordinary stomach tube fenestrated at one end Over these fenestrations is drawn a rubber tube or bag This is secured above and below the openings Over this is a silk bag to limit the distention of the rubber, and this in turn is covered with another layer of rubber The last two layers are secured about the stomach tube as was the first by tying with silk This may then be connected with a water tap, and the water running through the stomach tube and out the fenestrations distends the rubber bag, guarded by the silk bag, according to the force of the stream allowed to run in If the end of the stomach tube covered with the rubber bags is passed into the cardia while collapsed and the water is turned on, as the water distends the bag the cardia will be dilated This gives the patient considerable pain, and it may be a guide to the amount of distention and to the length of time dilatation is continued Plummer believes that pain is not a reliable symptom, and that the pressure should be measured Insertion of such a large contrivance may be difficult or impossible, so that preliminary dilatation with bougies is required

It is difficult to enter the cardia with even small bougies in some cases, and the string method used in dilatation of esophageal stricture is used The patient swallows an end of silk ligature Number 6 does very well A lead shot may be fixed on the end to facilitate swallowing The patient keeps on swallowing until 5 or 6 yards have been swallowed Then small metal olives on a flexible rod, the silk thread running through a hole entering the tip of the olive and passing out of the back, are pushed down the esophagus, and, guided by the silk ligature, are passed into the stomach These olives are gradually increased in size When one of sufficient size has been passed, a dilating

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128 Sippy, B W Paper read at a meeting of the American Medical Association, 1906, not published, quoted by Plummer<sup>15</sup>

129 Plummer (footnotes 15 and 16)

130 Oehler, J Treatment of Cardiospasm, *Munchen med Wchnschr* 69 1482 (Oct 20) 1922

bag is next used, which has a perforated olive at its tip. This is guided into the stomach in the same manner that the olives on the flexible rod were passed. With the bag in place, hydrostatic dilatation is possible.

Plummer has made use of a gage to record the water pressure that is being used. The pressure is expressed in terms of feet of water. Myers does not use a gage, but is guided by the pain experienced by the patient. Plummer's dilator is made up as follows. A stomach tube about 30 French is used. This is open at both ends. The end that is to be passed into the esophagus tapers slightly, and into this is fastened a piece of hollow metal tube about 3 cm long. This tubing has two indentations on the outside, one to permit fastening the stomach tube and one to permit fastening the rubber and silk bags. The end designed to project beyond the stomach tube has a screw thread, and onto this the perforated olive screws. A rather stiff woven silk stylet attaches to the metal tube inside the stomach tube, small enough not to interfere with the passage of water down the tube. This stylet is shorter than the stomach tube, but is long enough so that it can be grasped through the tube and used, thus giving rigidity to the tube and making its passage easier. To provide the water pressure a rubber tube is connected to the water tap. Objection to the Plummer dilator is that its stylet allows the operator to push the instrument into place regardless of minor obstruction. I have had 1 fatality from a perforated esophagus with this instrument which would not have occurred with a Lerch dilator, which consists of a rubber tube and bag without metal or a stylet on the end. When one attempts to push the rubber stomach tube it is not stiff enough to perforate the esophagus, but works its way along. On the other hand, it is impossible to force the Lerch instrument into some stomachs in which one might be successful with the Plummer instrument.

From 2 to 5 dilatations are made. Many patients are relieved by a pressure equal to a column of from 16 to 22 feet of water. In marked cases from 24 to 28 may be given. If a fissure or ulcer is present, one should dilate a little and then wait. The patient is cured if the esophagus functions normally ten days after any dilatation. About 25 per cent require a second stretching later. Vinson's mortality is 1 in 350 cases. Whatever method is used, it is a hospital procedure.

Straus<sup>68</sup> has also passed a spindle-shaped bag collapsed. It is then blown up and withdrawn. This was reported six years after the similar method of Russell. Starck<sup>84</sup> has an expanding dilator which he passes through the esophagoscopy under direct vision. Maydl<sup>131</sup> used this

131 Maydl, V. Treatment of Cardiospasm with Starch's Sound, *Casop lék česk* 67 877, 1925, abstr, *J A M A* 85:480 (Aug 8) 1925.



method with success in 5 cases. Huist<sup>50</sup> constructed mercury bougies. These are rubber tubes varying in diameter from thirty-three sixty-fourths to forty-six sixty-fourths inch and are each 31 inches long. Each bougie contains 1 pound and 5 ounces (595.3 Gm) of mercury. He has had but one case in which he could not pass the tubes. Lyon<sup>132</sup> treated a patient with bougies of increasing size, and followed this by a galvanic current and then a sinusoidal current.

It seems inevitable that an instrument will be devised less cumbersome and awkward than the hydrostatic dilator and with which the pressure can be more easily controlled. Possibly such an instrument has been devised by Zohlen<sup>133</sup>. I have had no experience with the Zohlen dilator, but it seems to be promising.

#### SUMMARY

An account of cardiospasm with dilatation of the esophagus is given, recounting the history, pathogenesis, contributing factors, pathologic changes, age, duration, sex, symptoms, esophagoscopy, roentgen study, complications, associated diseases, diagnosis, prognosis and treatment. A review of the literature and data from 13 personally observed cases are given.

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132 Lyon, B. B. V. A Consideration of Cardiospasm with Report of a Case, *Am J M Sc* **151** 389 (March) 1916.

133 Zohlen, J. P. A New Collapsible Esophageal and Cardiospasm Dilator, *Wisconsin M J* **28** 168 (April) 1929.

# MODE OF PRODUCTION OF THE FIRST HEART SOUND

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SAN FRANCISCO

The experimental observations on dogs' heart sounds here described were intended to cast further light on the relative importance of muscular and of valvular elements in the production of the first heart sound. The theory based on these observations seemed to conflict with the views of recent workers, particularly with those of Wolferth and Margolis in their excellent study of the variations of intensity of the first sound in heart block. The relation between auricular systole and the first sound is therefore described in some detail. It is believed that the theory offered gives a coherent explanation of all the phenomena noted in the study of the first heart sound <sup>1</sup>

## METHODS

Dogs anesthetized with a brand of chlorbutanol were subjected to midline thoracotomy, and respiration was artificially maintained. The heart sounds were recorded by a collodion Frank capsule from small tambours attached to the ventricular surface by short rigid levers. This is a modification of the method of Wiggers and Dean <sup>1a</sup>. The vibrations recorded resemble in form and amplitude those obtained with Frank capsules in the clinical study of heart sounds. Electrocardiograms were recorded from copper wire leads inserted in the shoulder and thigh muscles, through a 20 microfarad capacitance in series with the string galvanometer. Digifolin, injected directly into the ventricle, was used to produce ventricular tachycardia and fibrillation. Isometric ventricular contractions were obtained by putting a heavy cord, covered with petrolatum, around the atrio-ventricular groove and suddenly drawing it tight so as to prevent blood from entering or leaving the ventricles. When the ligature around the auriculoventricular ring

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1 Historical Note. The theory supported by the discussion in this paper was first stated, without adequate experimental evidence, by J. Rouanet, in a thesis, *Analyse des bruits du coeur*, given in Paris on Aug. 31, 1832. The following is my translation of some statements from page 8: "The shock of blood against the valves, or of valves against the heart wall, the shock which might result from two bodies colliding, is not the only cause of a valvular sound. From many experiments I have learned that any membrane, passing from flaccidity to tension suddenly, always make a sound. The auriculoventricular valves present conditions which are most favorable for the production of sound, they are thin and tough, and do not stretch, they pass instantly from the most complete flaccidity to sudden and violent tension."

1a Wiggers, C. J., and Dean, A. S., Jr. The Nature and Time Relations of the Fundamental Heart Sounds, *Am J Physiol* 42:476, 1917.

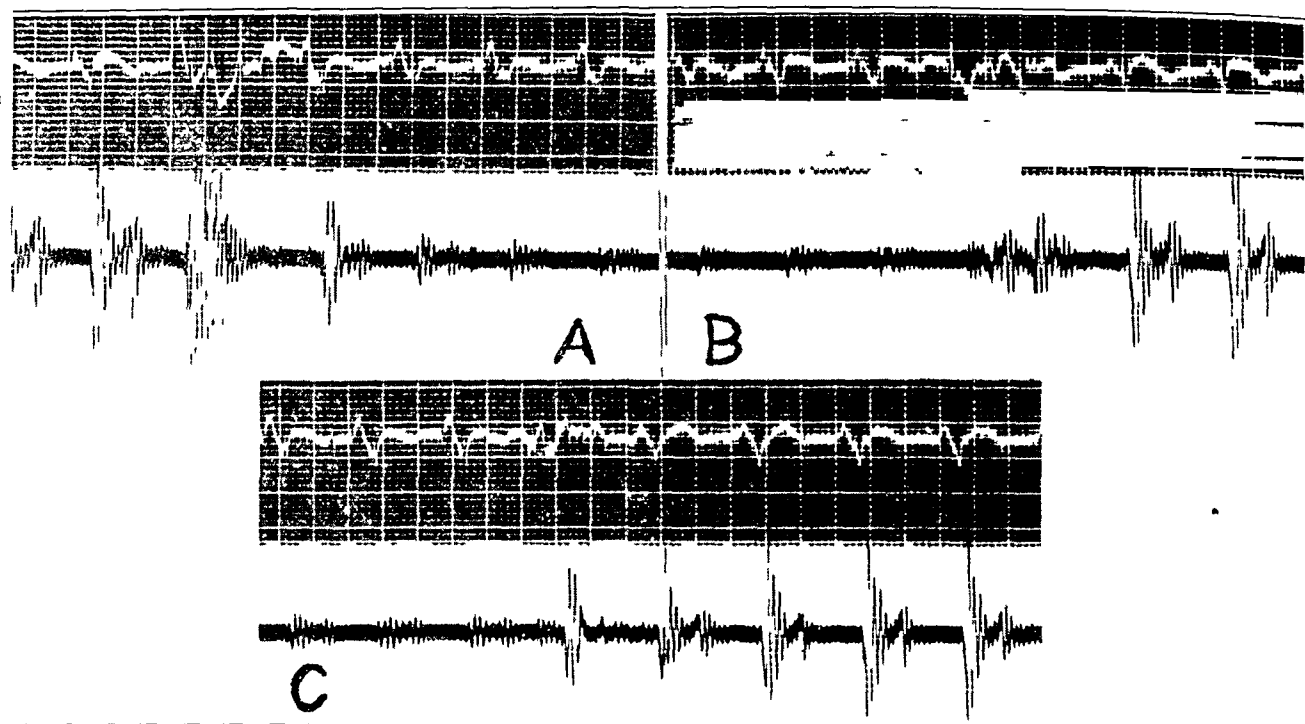


Fig 1—*A*, the effect of clamping off the venous flow to the heart, *B* and *C*, the effect of releasing venous inflow (dog 6)

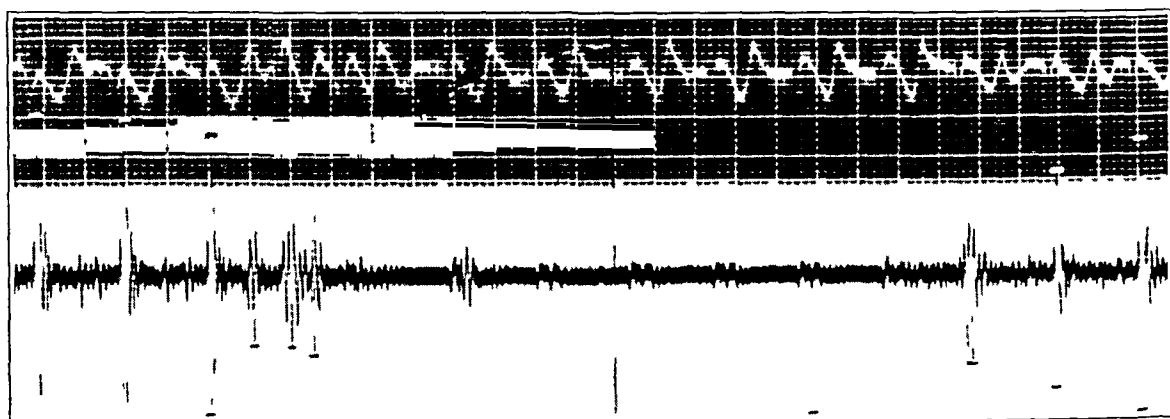


Fig 2—The effect of closing and opening the clamp on the venous inflow of the dog's heart on the intensity of the heart sounds (dog 9)

was tightened, the heart was sometimes caught full of blood, at other times, at the end of systole, it was small but still much larger than when venous filling was prevented. Tightening this ligature produced, in one instance, a high degree of auriculoventricular heart block. A rubber-faced, spring-bladed enterostomy clamp was used to close the openings of the great veins into the auricles. One blade was passed between the auricles and the pulmonary artery and aorta, the other was brought behind the apex of the heart, and the clamp, nearly closed but permitting normal circulation, was left in place behind the auricles. By opening and closing the clamp, venous filling could be started or stopped at will. When the clamp was closed, the heart became small and bloodless, but contracted vigorously.

*Sum of the Amplitudes of the Three Largest Vibrations of the First Heart Sound Records, in Different Dogs and Under Various Conditions of Cardiac Activity*

Dogs	Ventricular Tachycardia, Mm	Rapid Ventricular Fibrillation, Mm	Slow Ventricular Fibrillation, Mm
	43	0	0
	Venous Inflow Normal	Venous inflow Shut Off	Venous Inflow Released
Dog 4	31	25	25
Dog 6	40	25	37
Dog 7	34 42 37	15 15 15	34 34 36
Dog 9	52 63 38 34	15 40 20 15	37 51 47 36
Dog 10	23 22	10 10	26 30
Dog 11	22 31	10 25	19 34
Average	36	18	34.5
	Normal Flow	Ligature Around Auriculo- ventricular Groove	
Dog 10	31	05	
Dog 11	25	35	
Average	28	20	

## RESULTS

During ventricular tachycardia the first sound was loud, but with the onset of fibrillation all sounds ceased. Violent incoordinate muscular activity was visible, the muscle was under some tension and the heart maximally dilated, but such muscular activity produced no sounds comparable to those audible with normal heart action (table).

When the heart beat isometrically the sound production either ceased entirely or was greatly diminished (table). When the heart was empty, because of impaired venous return, the heart sounds entirely ceased but some vibration due to the violent mechanical movement of the receiving tambour remained (figs 1 and 2). As seen in the table

clamping off the venous inflow, in thirteen attempts on five dogs, gave an average reduction of 95 per cent in the amplitude of vibrations produced in early systole, while the ligature around the auriculoventricular ring reduced the amplitude by 93 per cent. Not only was the amplitude diminished, but the recorded vibrations were so different in form from those recorded from the hearts before circulatory conditions were altered as to leave no doubt that in clamped-off or ligatured hearts the recorded vibrations were inaudible mechanical effects of ventricular movement.

#### COMMENT

Extensive discussions and bibliographies on the theories and experimental observations on the first heart sound have been given recently by Schutz<sup>2</sup> and by Frey.<sup>3</sup> Five theories, with variations, have been advanced in explanation of these vibrations. Briefly, the sound is supposed to originate in the closure of the auriculoventricular valves, in the friction of contracting ventricular muscle, in the change in tension in the aorta and pulmonary artery, in the change in tension in the coronary vessels (Laurell,<sup>4</sup> 1931) and finally, according to the thesis accepted by both Schutz and Frey, in the physical changes in tension of the ventricles during the rise of intraventricular pressure. The customary explanation given in recent texts on heart disease and on physical diagnosis is that the first sound is both muscular and valvular in origin, but it is not stated how the muscle or valves set up audible vibrations. No theory has been elaborated to account for the accentuated heart sound heard in some cycles in cases of complete heart block or in cases of mitral stenosis.<sup>5</sup>

2 Schutz, E. Experimentelle Untersuchungen über die Entstehung der Herztöne, *Ztschr f d ges exper Med* **77** 348, 1931.

3 Frey, W. Die Ursachen der Entstehung der Herztöne, in *Handbuch der normalen und pathologischen Physiologie*, Berlin, Julius Springer, 1926, vol 7, pt 1, p 292.

4 Laurell, H. Die Coronarkreislauf ein übersehener Faktor bei der Deutung der Druck- und Schallphänomene im Herzen, *Upsala Lakaref orh* **36** 133, 1931.

5 Historical Note. In 1841 James Hope (*London M Gaz* **30** 310, 1841) wrote of his previous experimental work, described in an appendix to the second (1835) edition of his "Treatise": "The first sound was shown by evidence verging upon demonstration to be occasioned partly by sudden extension of auricular valves and chordae tendineae, and partly by similar violent extension of the muscular walls at the moment the valves close." This is the earliest statement of the theory now held in Germany. In 1851, G. B. Halford (*Lancet* **2** 593, 1851) first performed the experiment which demonstrated the absence of a muscular element in the first heart sound, with a technique not unlike that used in the experiments of this paper. Halford wrote: "The superior and inferior vena cava and the pulmonary veins at the entrance to the left auricle were tightly compressed between the fingers. The heart continuing its action, a stethoscope was again applied, and neither first nor second sound was heard." Halford's crucial experiment is not referred to by subsequent investigators, although others observed similar phenomena.

From the experimental evidence summarized in the papers just mentioned it is quite clear that the contraction of ventricular muscle does not, in the intact heart, produce an audible vibration although according to unpublished work of Wiggers and Dean<sup>6</sup> vibrations can be recorded from strips of cat ventricle. The experiments reported in this paper demonstrate that vigorous ventricular systole may produce no sound. Sound production in the root of the aorta or in the coronary vessels may occur, but since the main vibrations of the first sound occur before the pressure changes in these vessels it is unlikely that they contribute any important element. The theory accepted by Schutz and Frey, namely, that the sudden change in tension of the structures in the ventricular walls causes audible vibrations, includes the auriculo-ventricular valves as part of the vibrating mass. As given by Schutz, this theory is stated thus:

With the suddenly developing contractile process of the myocardium, the active tensing of the elastic heart-wall around its incompressible content releases vibrations of audible frequency (and intensity). These vibrations can be experimentally demonstrated in relation to the first heart sound, both on the ventricular walls and in the curves of intra-auricular pressure near the auriculoventricular valves.

This theory, as given by Schutz, Frey and others, ignores the accentuation of the first sound in mitral stenosis and in the ventricular beats, in cases of heart block, which occur shortly after auricular beats. However, some such explanation seems to be accepted by Wolferth and Margolies<sup>7</sup> to account for these clinical phenomena. The validity of such an explanation will be considered shortly, but it is obvious that, according to this theory, sound production should be quite normal in the isometrically contracting heart if the ventricular cavities are filled. The experiments on the dogs whose ventricles were tied off by a ligature in the auriculoventricular groove show that sound is not necessarily produced by the "tensing of the heart-wall around its incompressible content." Experimental findings, so at variance with theory, seem to justify the rejection of the theory as incorrect or incomplete. This leaves as a possible explanation only the valvular origin of the first heart sound. It is apparent that the sounds which originate in valves do not come from the mere closure of the valve but from the sudden tensing of the fibers. Thus the explanation of Schutz and of Frey might be accepted, restricting the region in which the vibrations arise to the structure associated with the valves but excluding the muscle mass. In the dog's heart, ligatured at the auriculoventricular ring the valvular structures, being supported by the muscle drawn in about them

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<sup>6</sup> Wiggers, C. J. *Modern Aspects of the Circulation in Health and Disease*, Philadelphia, Lea & Febiger, 1923, p. 319.

<sup>7</sup> Wolferth, C. C., and Margolies, A. *The Influence of Auricular Systole on the First Heart Sound and the Radial Pulse*. *Arch. Int. Med.* **46**: 1048 (Dec.) 1930.

by the ligature, no longer are tautened during systole, and hence no longer set up audible vibrations. If this explanation is correct, the vibrations recorded by Schutz from the surface of the ventricles arose, not in the muscle, but in the valves and were transmitted to the ventricular walls as well as to the blood in the auricles, where similar vibrations were apparent in the pressure curve.

Palfrey<sup>8</sup> and Cabot<sup>9</sup> have noted the similarity between the first sound and that made when a handkerchief, held with one edge in either hand, is suddenly drawn taut. Palfrey, like Schutz, ascribed the first sound to a similar tensing of the ventricular walls. But while it is true that sudden changes in fine fibers, like a string, a handkerchief or even a bit of canvas, will give rise to audible vibrations, it is almost impossible to cause such noises with a piece of thick carpet or with strips of meat as thick as the wall of the left ventricle. That the first sound originates entirely in thin fibrous sheets or bands would be suggested by these simple observations. That it is due to the tensing of the auriculoventricular valves, in a way very similar to the noise produced with the handkerchief in Palfrey's experiment, is suggested by the importance of auricular systole in determining the intensity of the first heart sound.

The variation of the intensity of the first heart sound in cases of complete heart block has been known for many years, frequently recorded in phonocardiograms and discussed at some length by Lewis<sup>10</sup>. In the most complete study, that of Wolferth and Margolies, it was concluded that the "position of the mitral leaflets at the beginning of ventricular systole" was important in modifying the first sound. Wolferth and Margolies<sup>7</sup> observed that intense first sounds were not associated with more vigorous radial pulse waves, and therefore probably not with more vigorous muscular contractions. They did not suggest that the sound originated in the mitral valve, but apparently adhered to the classic theory that it is partly muscular and partly valvular. The reason for less intense sounds, they suggested, was that if ventricular systole occurred when the mitral valve was open, "slight regurgitation might occur, thus retarding the development of intraventricular tension. If, however, the leaflets happened to be near a position of closure at the beginning of ventricular systole, little or no regurgitation might be expected to take place, thus permitting a more rapid rise of intraventricular tension and consequently a louder first sound." Dean<sup>11</sup> has

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8 Palfrey, F. W. The Cause of the First Heart Sound, *New England J Med* **200** 917, 1929.

9 Cabot, R. C. *Physical Diagnosis*, New York, William Wood & Company, 1930, p. 172.

10 Lewis, T. *The Relation of Auricular Systole to Heart Sounds and Murmurs, Lectures on the Heart*, New York, Paul B. Hoeber, Inc., 1915, p. 53.

11 Dean, A. L., Jr. Movement of the Mitral Cusps in the Cardiac Cycle, *Am J Physiol* **40** 206, 1916.

shown that the auriculoventricular valves move from one-third to one-half the distance from wide open to completely closed for a brief moment at the end of auricular systole, but nothing approaching closure of the valves occurs between the onset of the P wave and ventricular systole, even when the P-R interval is 0.24 second. Therefore, the accentuation of the first sound during the interval from 0.05 to 0.23 second after P cannot be due to the auriculoventricular valves being closed.

The explanations of Schutz and of Frey and the analogy offered by Palfrey and Cabot stress the importance of suddenly tensing fibers which were previously under no tension. According to the valvular theory, sound production is due to the sudden rise in tension of the auriculoventricular valves and associated thin fibrous structures occurring when these fibers are slack. If the valves are not only closed but under slight tension from the ventricular side, little or no noise will be caused by further sudden increase in tension. Here, the analogy with the handkerchief is pertinent. If a string or a piece of cloth like a handkerchief is held a little slack between the two hands, and the slack taken out quickly by a light pull, a noise quite similar to the first sound is produced. However, if the slack be taken out gradually by a light pull and then the tension quickly raised even with great force, no noise results. By analogy, whenever ventricular systole occurs at a time when intra-auricular pressure is high and the auriculoventricular valves are not only open but pressed toward the ventricle so as to leave the fibers slack, a sound should arise from suddenly taking the slack out of these thin fibrous structures. If intra-auricular pressure is relatively low, or the ventricle is distended with blood, the auriculoventricular valves may have the slack taken out of them by the relatively high intra-ventricular tension, and hence little or no noise will result with the rise of tension during ventricular systole.

The relation of auricular systole to the intensity of the first sound caused by ventricular contractions occurring at various intervals thereafter is indicated in figure 3. The time relations of auricular pressure and ventricular filling were obtained from Lewis<sup>12</sup> and Wiggers<sup>13</sup>. One of Wiggers' figures<sup>13a</sup> is particularly important, as it shows the effects of a blocked auricular systole without any subsequent ventricular contraction. The intensity of the first sounds occurring at various intervals after the P wave of the electrocardiogram was obtained from three cases recorded in this clinic and those reported by Wolferth and

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12 Lewis, T. Mechanism and Graphic Registration of the Heart Beat, London, Shaw & Sons, Ltd., 1925, p. 47, fig. 24.

13 (a) Wiggers, C. J. Die pathologische Physiologie des Kreislaufs bei Klappenerkrankungen des Herzens, *Ergebn. d. Physiol.* **29**: 262, 1929, fig. 2b, (b) footnote 6, p. 101, fig. 30.



Margolies<sup>7</sup> and by Schellong<sup>14</sup> It is obvious that the intensification of the first sound occurs only when auricular pressure and flow into the ventricle are at their peak at the instant the first sound occurs and that faint sounds occur when rate of outflow from the auricle is low. It should be noted that the second period of accentuation occurred only in young hearts, with relatively rapid ventricular rates and of normal size. In older, slower beating and more diseased hearts the degree of ventricular dilatation was probably sufficient to take the slack out of the auriculoventricular valves at all times except during auricular systole.

The conditions for sound production in mitral heart disease are of particular importance. If the mitral valve is extremely incompetent, a murmur may entirely replace the first sound. In other cases of mitral endocarditis the first sound is accentuated. This is more likely to occur

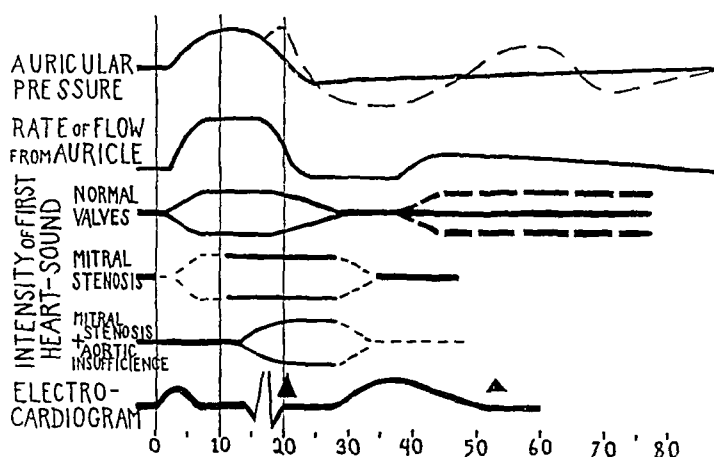


Fig. 3—The intensity of the first heart sounds occurring at various intervals after the P wave is plotted below the curves of auricular pressure and rate of flow through the auriculoventricular valves (time in hundredths of a second after the onset of P). The dotted line of auricular pressure represents time when ventricular systole occurs normally. The heavy lines indicate pressure and flow with blocked auricular systoles. The normal electrocardiogram and the position of the normal first (large arrow) and second (small arrow) heart sounds are also shown for comparison. The second period of intensification of the first sound in hearts with normal valves, indicated by interrupted lines, has rarely been heard or recorded. It occurred in cases 4 and 5 of Wolferth's and Margolies' series.

if the valve is greatly constricted. Three factors may contribute to this accentuation. In the first place, the ring to which the vibratile fibers attach is rigid, and the taking out of the slack is not buffered by any yielding of these points of attachment. Secondly, the degree of ventricular distention is usually slight, so that an optional degree of slackness may be present. In normal hearts the peak of the intra-auricular pressure curve may be passed shortly before ventricular systole so that some slack may be taken up before systole occurs. In mitral

<sup>14</sup> Schellong, F. Mitralstenosengeräusch bei Leitungsstörung, *Klin. Wchnschr.* 8: 2042, 1929.

stenosis the discharge from the auricle is retarded, and the peak of intra-auricular pressure may occur later or be sustained longer than in normal hearts, so that with normal or prolonged conduction time ventricular systole occurs when the mitral valve is still maximally displaced toward the ventricle. It is not possible to state which factor or factors are of greatest importance in causing the accentuated "mitral" first sound, but it is of interest that in mitral stenosis the period of accentuation, in cases with variable P-R intervals, is more prolonged than in normal hearts. Both in Wolferth and Margolies' and in Schellong's<sup>14</sup> cases of mitral stenosis, accentuation was still present when the P-R interval was 0.23 second, while in normal hearts accentuation diminished when the P-R interval was more than 0.14 second in most cases and 0.20 second in all cases. This would seem to favor the prolonged forceful auricular systole as the chief explanation for the accentuated first sound in cases of mitral stenosis with normal conduction. In Wolferth's and Margolies' five patients without lesions of the valve, first sounds were accentuated when the P-R intervals were 0.12 second, with P-R intervals of 0.14 second the accentuation was distinctly less in three cases. As most adults have P-R intervals of 0.14 second or more, this would indicate that the first sounds would be louder if the P-R interval were shortened or if auricular systole lasted 0.02 second longer. A prolongation of the peak of auricular systole by from 0.02 to 0.04 second in the presence of mitral stenosis seems quite probable and is perhaps the chief factor in the accentuation of the first sound.

In this connection another observation of Wolferth and Margolies must be noted. In their case of mitral stenosis and aortic insufficiency, not only was the end of the period of accentuation later than in normal hearts, but the onset of accentuated first sounds occurred much later. The normal first sound is accentuated if it occurs 0.02 second after P, but in this patient no accentuation was apparent until the interval between onset of P and the first sound was 0.13 second. The maximum accentuation, which occurs in normal hearts as early as 0.05 second after P, was found in this case only 0.21 second after P. Margolies and Wolferth suggested that this was due to the mitral stenosis, and quoted Schellong's paper in support of this thesis. An examination of the curves published by Schellong<sup>14</sup> does not bear out this interpretation. The three accentuated sounds are in three different strips with second sounds of different amplitudes. But from a comparison of the degree of accentuation of the loudest and faintest sounds on each strip, it is apparent that the accentuation is nearly as great with a P-R interval of 0.05 second as with one of 0.17 or 0.23 second. In other words, accentuation begins later in a patient with aortic insufficiency plus mitral stenosis, but not in pure mitral stenosis. This suggests that the regurgitation of blood into the left ventricle prolongs

the intervals which must elapse before auricular systole raises the intra-auricular pressure above that in the left ventricle, and hence the period before the auriculoventricular valves are slack enough to permit accentuated first sound production. This is in agreement with the experimental observations of Wiggers,<sup>15</sup> who found that aortic regurgitation could alter the outflow through the mitral valve.

#### SUMMARY

Experiments on the exposed hearts of dogs demonstrate that there is no muscular element in the first heart sound, and that ventricular systole produces no audible vibrations, in either empty or full hearts, if tensing of the auriculoventricular valves is prevented.

A comparison of the pressure changes in the auricles and the rate of outflow through the atrioventricular valves with the period at which first sounds are accentuated by a previous auricular systole shows the importance of the position of the auriculoventricular valves in determining the loudness of the first sound. If the valves are closed and intraventricular pressure about as high as that in the auricle, ventricular systole causes only a faint sound, if the valves are slack and displaced toward the ventricle by the rush of blood through them, ventricular systole produces a loud first sound.

#### CONCLUSION

The first heart sound is due to suddenly putting under high tension the previously slack fibers of the auriculoventricular valves. If the valves are closed and the slackness taken up gradually before ventricular systole occurs, the intensity of the sound is greatly diminished. The factors determining loudness of the first sound are, therefore, the degree of tension in the valves when ventricular systole occurs and (less important) the rate of rise of intraventricular tension.

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15 Wiggers, C. J., and Green, H. Experimental Aortic Insufficiency. Regurgitation Maximum and Mechanisms for Its Accommodation Within Mammalian Ventricle, *Proc Soc Exper Biol & Med* **27** 599, 1930. Wiggers, C. J., and Maltby, A. B. Hemodynamic Factors Determining the Characteristic Changes in Aortic and Ventricular Pressure Pulses in Experimental Aortic Insufficiency, *Am J Physiol* **97** 689, 1931.

# CYTOPLASMIC CHANGES IN CIRCULATING LEUKOCYTES IN INFECTION

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The severity of infection can be estimated by a study of the cellular elements of the peripheral blood stream. The number of circulating leukocytes and the differential percentage of each type have until now been given the greatest attention. It is accepted that a leukopenia in a severe infection, which usually induces a marked leukocytosis (pneumonia), often forewarns of a poor or fatal prognosis. On the other hand, there are many systemic infections in which leukopenia is the rule but nevertheless the prognosis in general is good. Thus, the quantitative estimation of leukocytes certainly appears not to be the most important factor in the gaging of the prognosis.

The differential count varies with the different types of infection. In allergic infections, an eosinophilia may be present, in tuberculosis, a monocytosis is usually found, in very severe suppurative infections, myelocytes are noted, in subacute bacterial endocarditis (*Streptococcus viridans*), small numbers of macrophages may be found in the peripheral blood, especially if the blood is obtained from the lobe of the ear.

Arneth<sup>1</sup> directed attention to variations in the nuclear configurations of the granulocytes. His method of classifying such variations was cumbersome and too complicated for general application in the routine clinical laboratory. Schilling<sup>2</sup> devised a simplified scheme for tabulating the various forms of the granulocytic cells, namely, the myelocytes, the young polymorphonuclears, the staff (band) polymorphonuclears and segmented polymorphonuclears. The relative percentage of each in the blood of a normal adult is given as follows: myelocytes, none; young polymorphonuclears, 1 per cent; staff polymorphonuclears, from 1 to 4 per cent; and segmented neutrophilic polymorphonuclears, from 60 to 70 per cent. In infections, there is usually an increase in the young and staff or band forms, which changes Schilling designated as "shift to the left." A somewhat simpler method of designating

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1 Arneth, J. Die neutrophilen Leukozyten bei Infektionskrankheiten, *Deutsche med. Wchnschr.* **30** 54, 1904, *Die qualitative Blutlehre*, Leipzig, Dr. Werner Klinkhardt, 1920.

2 Schilling, V. *Das Blutbild und seine klinische Verwertung*, ed. 7-8, Jena, Gustav Fischer, 1929.

polymorphonuclear cells was suggested by Pons and Krumbhaar.<sup>3</sup> They divided the polymorphonuclear cells into nonsegmented and segmented types. The severity of infection may furthermore be reflected by changes in the polymorphonuclear cells. Basophilic cytoplasmic granules, which have been designated as "toxic granules,"<sup>4</sup> appear. They are numerous, small in size, and rarely situated in the nuclear zone. These characteristics distinguish them from the granules of the basophilic polymorphonuclear cells. In addition, the entire cytoplasm, in severe infections, may show affinity for the basophilic stain (fig 1). Furthermore, the segmented polymorphonuclear leukocytes occasionally show vacuoles in the cytoplasm (fig 2). The presence of toxic granules and the degeneration of the cytoplasm of the granulocytic cells have been emphasized in the German literature, and more recently in this country by Rosenwasser and Rosenthal,<sup>5</sup> Kugel and Rosenthal<sup>6</sup> and Rosenthal and Sutro.<sup>7</sup>

So far, all such studies have been made with the use of special stains or buffered solutions, with either Wright or Jenner-Giemsa stains. In this study, which was undertaken in the hope of applying the investigation of cytoplasmic changes to routine examination, stock Wright stains were used. The air fixed slide was stained for one minute, and distilled water was added for three minutes. The slide was dried in air and examined with the ordinary oil immersion objective. In order to settle all doubts and to exclude the possibility that precipitated stain

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3 Pons, C, and Krumbhaar, E B. Studies in Blood Cell Morphology and Function. III. Extreme Neutrophilic Leukocytosis, with a Note on a Simplified Arneth Count, *J Lab & Clin Med* **10** 123, 1924.

4 Cesaris-Demel, A. Ueber die morphologische Struktur und die morphologischen und chromatischen Veränderungen der Leukozyten, auf Grund von Untersuchungen nach der Methode der Vitalfärbung des Blutes, *Virchows Arch f path Anat* **195** 1, 1909. Turk, W. Vorlesungen ueber klinische Haematologie, Vienna, W Braumueller, 1912. Naegeli, O. Blut-Krankheiten und Blutdiagnostik, ed 4, Berlin, Julius Springer, 1923. Alder, A, and Schleip, K. Atlas der Blut-Krankheiten, ed 2, Berlin, Urban & Schwarzenberg, 1928. Gloor, W. Die klinische Bedeutung der qualitativen Veränderung der Leukozyten, Leipzig, Georg Thieme, 1929. Mommsen, H. Die Granula der polymorphkernigen feingekornen Leukozyten unter normalen und pathologischen Verhältnissen ihre gesetzmässigen Beziehungen zum Ablauf akuter Infektionen, *Ztschr f d ges Exper Med* **65** 287, 1929, Die Pathologische (toxische) Granulation der feingekornen Leukozyten, ihre objektive Erkennung und praktisch klinische Verwertung, *Klin Wchnschr* **42** 2420, 1929.

5 Rosenwasser, H, and Rosenthal, N. The Blood Picture in Otitic Infections, *Arch Otolaryng* **14** 291 (Sept) 1931.

6 Kugel, M A, and Rosenthal, N. Pathological Changes in Polymorphonuclear Leukocytes During Progress of Infections, *Am J M Sc* **183** 657, 1932.

7 Rosenthal, N, and Sutro, Charles J. *Am J Clin Path* **3** 181 (May) 1933.

was being interpreted as granules, the patient's blood was placed on one portion of the slide and blood from a healthy control was smeared on another portion of the slide. Thus, the control and unknown blood



Fig 1—*Streptococcus peritonitis* (Wright stain) Toxic granules are seen in all the polymorphonuclear cells (absent in the control slide)



Fig 2—Lobar pneumonia (Wright stain) Toxic granules and vacuoles are shown. The vacuoles are particularly prominent in the lowermost leukocyte

are stained together. All difficulty in interpretation of the granules is definitely settled.

The present report is based on a study of about two hundred cases. The hemoglobin determination, red cell count, leukocyte count and differential studies were made. The polymorphonuclear cells were tabu-

lated as nonsegmented and segmented, according to the method of Pons and Kumbhaar. The results were tabulated as shown in the accompanying table, according to the suggestion of Kugel and Rosenthal.

The "degenerative index" enables one, more or less, to judge accurately the severity of the infection or intoxication from which the patient is suffering. Illustrative group cases given here show the value of estimating the degenerative index.

#### REPORT OF CASES

CASE 1—Dr. T. was admitted to the hospital on May 7, 1932, complaining of severe pain in the lower right side of the chest and of fever. During 1922, for a period of four months, he had mild pains in the chest and profuse expectoration of foul sputum. Prior to 1922, he had suffered considerable exposure to x-rays and had lost one of his fingers due to a severe roentgen burn. A roentgenographic

#### Hemogram \*

	Nontoxic	Toxic	Total
Neutrophil polymorphonuclear cells			
Nonsegmented	15	25	40
Segmented	30	20	50
Total	45	45	90
Lymphocytes	8		
Monocytes	2		
Eosinophilic polymorphonuclears			
Basophilic polymorphonuclears			
Myeloblasts			
Myelocytes			
Macrophages			
		Toxic polymorphonuclear cells	45 1
		Total polymorphonuclear cells	90 2
		Degenerative index	= ++

\* The number of toxic polymorphonuclear cells divided by the total number of polymorphonuclear cells is the "degenerative index."  $1 = 4$  plus  $\frac{3}{4} = 3$  plus  $\frac{1}{2} = 2$  plus, and  $\frac{1}{4} = 1$  plus. When the results are in between these figures, the "degenerative index" is approximate. However, a four plus is never diagnosed, except when all the cells show basophilic granules.

plate of the patient's chest on admission revealed a solid mass extending from the apex to the base on the right side, almost suggesting solid carcinoma. The leukocyte count was 12,000, 88 per cent of polymorphonuclears were present and there was a four plus degenerative index. The presence of these toxic granules in all polymorphonuclear cells suggested severe infection or an ulcerative type of carcinoma. Postmortem examination one day later showed a lobar pneumonia which extended from the apex to the base.

It is accepted that toxic granules are found in all cases of lobar pneumonia in adults with or without pleural effusion, and in the absence of toxic granules it is hazardous to make a diagnosis of lobar pneumonia.<sup>7</sup> However, in pulmonary diseases, such as mild tuberculosis, rheumatic fever, draining lung abscess or in nonulcerating carcinoma, toxic granules are usually absent, and give at the most a one plus index. It is interesting that patients receiving deep roentgen therapy will often show a four plus index owing possibly to protein destruction and to a marked absorption. Cases of ulcerating carcinomas will also show high degenerative indexes.

CASE 2—E B, a girl, aged 19, was admitted to the hospital with a history of terrific lower abdominal pain and irregular menses. Blood examination prior to operation revealed a slight leukocytosis of 12,000, and a slight increase in the polymorphonuclear neutrophils to 75 per cent, but the absence of toxic granules. Two days after operation, at which a chronically inflamed appendix was removed, there developed a sudden rise in temperature to 104.8 F. The blood count showed 8,000 leukocytes, but 29 per cent were segmented polymorphonuclear cells, and the degenerative index was two plus (April 12). On April 13, the white count was 6,000, with 45 per cent nonsegmented polymorphonuclear cells and an index of four plus. On April 18, the white count rose to 18,000, the nonsegmented cells were 40 per cent, and the degenerative index was four plus. On April 20, another count showed 13,700 leukocytes, 35 per cent nonsegmented polymorphonuclear cells and four plus toxic granules. The patient died, and during her stormy clinical course, showed definite evidences of peritonitis. A blood culture four days before death was positive for the hemolytic streptococcus.

It is important to note that in acute abdominal conditions, when the lesion is still localized, as for instance, in acute appendicitis or in acute cholecystitis, toxic granules in the cytoplasm of polymorphonuclear cells are unusual. However, when they appear complications such as pyelophlebitis, ruptured abscess, peritonitis or bacteremia must be suspected. In children with undiagnosed intra-abdominal complaints, but with a blood picture showing toxic granules in all polymorphonuclear cells, pneumonia, bacteremia or possible metastatic septic foci must be suspected.

CASE 3—A boy, aged 6 years, was admitted to the hospital with a diagnosis of bilateral suppurative ethmoiditis. Physical examination revealed bilateral swelling of the periorbital tissues and tenderness over the ethmoid regions. A blood count showed 17,900 leukocytes, and a differential count showed 20 per cent nonsegmented and 56 per cent segmented polymorphonuclear cells, 21 per cent lymphocytes and 3 per cent monocytes. The degenerative index was four plus. Blood culture was positive for *Streptococcus viridans*. A radical frontal sinusectomy was performed. The pus obtained from the ethmoid area contained green-producing streptococci. Seven days after operation, the leukocyte count was 11,400, and there were 61 per cent polymorphonuclear cells and 39 per cent lymphocytes. Basophilic toxic granules were absent. The patient made an uneventful recovery.

In this case, as so often happens in cases of bacteremia, a four plus degenerative index was noted even before the results of the bacteriologic examination was reported. Most of the protracted generalized infections, with the exception of subacute bacterial endocarditis and miliary tuberculosis cause the appearance of toxic granules, and the blood cultures show bacteria less constantly. However, in the pre-agonal state, toxic granules may be found in practically all infections, as in a case of subacute bacterial endocarditis a two plus degenerative index was observed two days prior to death, the explanation for this was evident at postmortem examination, for in addition to the subacute bacterial endocarditis bronchopneumonia was found. In very septic patients without toxic granules in the leukocytes and with negative serum agglu-



mination tests and negative blood cultures, one should think of miliary tuberculosis, subacute endocarditis (bacteria-free) or rheumatic fever

CASE 4—V C, a girl, aged 12 years, was admitted to the hospital with the history of a painful discharging ear of one week's duration. There had been chills and fever ranging from 102 to 104 F. On April 11, one day prior to mastoidectomy, the total leukocyte count was 19,000 with 82 per cent polymorphonuclear cells, but no toxic granules were present. Two days after the operation, the temperature was still 104 F, and the leukocyte count dropped to 14,700 cells per cubic millimeter, but the differential count showed 14 per cent nonsegmented forms and 54 per cent segmented forms. At this time, all of the polymorphonuclear cells showed toxic granules. The high degenerative index suggested the presence of either a sinus thrombosis or pneumonia, or possibly both. Blood cultures were sterile on two occasions. On April 15, roentgen studies showed pneumonia of both upper lobes. On April 22, blood examination revealed 27,800 white cells with 91 per cent polymorphonuclear cells. The degenerative index was still four plus. The steady high index intimated a very poor prognosis. The patient died on April 30.

Postmortem examination revealed a free sigmoid sinus without any evidence of thrombosis. In the lungs, gangrenous metastatic pyemic abscesses were found in all lobes, especially on the left, with multiple perforations into the left pleural cavity and the presence therein of an empyemic foul-smelling mass of pus. In addition, there was a complete compression atelectasis of the left lower lobe and emphysema of the right lung with fresh abscesses. A small interlobar empyema was found. An embolus was seen in one of the bronchial arteries.

This case emphasizes the fact that the degenerative index may be four plus, and yet no positive blood culture could be obtained in a case that was definitely one of bacteremia. The blood in otitis media or mastoiditis shows few or no toxic granules. A sudden appearance of toxic granules in such cases signifies an overwhelming infection, such as sinus thrombosis, pneumonia or metastatic pyogenic foci.<sup>8</sup>

CASE 5—H P, aged 30, presented symptoms and signs of chronic cholecystitis. Blood examination prior to operation revealed nothing unusual. Three days after the laparotomy, the temperature rose suddenly to 103 F. The blood count showed 43,000 leukocytes per cubic millimeter, with 92 per cent polymorphonuclear cells and a three plus degenerative index. Six days later, the abdominal wound broke open from a necrotizing infection. After proper surgical treatment, the leukocytes became reduced to 32,000 and the degenerative index was two plus. Five days later, the leukocyte count was 9,800, and all toxic granules disappeared. The patient made an excellent recovery. Recovery was anticipated because the degenerative index became reduced, rather than four plus, but nevertheless the patient had a stormy course.

Case 5 may now be contrasted with case 6.

CASE 6—O C, a boy, aged 11 years, had a scar due to an old burn on his right knee. A pedicle skin flap plastic operation was done. Blood examination before operation revealed nothing abnormal. Postoperatively, the temperature rose suddenly to 105 F. Blood examination at this time showed a leukocyte count of 44,000,

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<sup>8</sup> Footnotes 5, 6 and 7

with 19 per cent nonsegmented forms and 69 per cent segmented forms, and the absence of toxic granules. At no time did the patient appear desperately ill. Forty-eight hours later, the patient was able to get out of bed, in spite of a leukocyte count of 28,100.

In retrospect, these two cases corroborate the importance of looking for toxic granules, for in spite of the fact that both patients had high leukocytosis, their clinical courses were divergent, as the second patient did not show toxic granules.

CASE 7—A G came to the hospital complaining of a swollen left leg, which existed for two months. Physical examination revealed a brawny indurated left leg. Prior to operation, the blood examination showed nothing unusual. Laparotomy revealed a large retroperitoneal tumor, which on microscopic examination was carcinoma. Five days after the operation, the temperature rose to 105 F. The wound revealed the presence of foul-smelling necrotic tissue. All subsequent dressings showed a sanguineous discharge and contained tissue masses. The absorption in association with the tissue necrosis was probably of importance in the induction of a three plus degenerative index. With cessation of discharge from the wound and the return of the temperature to normal, the degenerative index became reduced to one plus. The patient was much improved and was discharged one week later.

#### CONCLUSION

In a study of two hundred cases in which the blood was investigated for toxic granules, it was found that the continued presence of a four plus degenerative index would indicate a serious prognosis. A four plus degenerative index in cases in which bacteremia or pyemia is suspected points to generalized infection in spite of a negative blood culture. In local infections (mastoiditis, acute appendicitis, etc.) without complications, there will be no toxic granules, or at most the degenerative index will be one or two plus. However, should these conditions be complicated by bacteremia or peritonitis, toxic granules appear in many or all of the polymorphonuclear cells.

# SYPHILIS OF THE STOMACH

WITH SPECIAL REFERENCE TO THE SIGNIFICANCE OF SPIROCHETES

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The presence in gastric lesions of spirochetes having the morphologic characteristics of *Spirochaeta pallida* is generally considered proof positive that the underlying disease is syphilitic. Even when the histologic changes are not syphilitic in type the occurrence of these spirochetes, according to current view, stamps the process as syphilitic. The correctness of these statements can be readily affirmed by reference to almost any text or periodical dealing with gastric syphilis. Luria,<sup>1</sup> whose monograph represents the most comprehensive and recent survey of the subject, after emphasizing the difficulties in distinguishing, by histologic means alone, syphilitic from other gastric lesions, wrote

It would be particularly valuable, therefore, if one were to succeed in finding spirochetes in microscopic sections of the stomach, especially in specimens obtained by operation. Such a finding furnishes naturally unequivocal proof of the syphilitic origin of the pathological process and helps to interpret the histological picture in questionable cases.

The propriety of attaching diagnostic significance to the mere presence of spirochetes morphologically resembling *Spirochaeta pallida* has been subjected to but limited scrutiny. In 1928, in collaboration with Dr. F. G. Dyas,<sup>2</sup> I reported a case of gastric syphilis in which spirochetes were found but were not considered syphilitic. It was pointed out at that time that the presence of spiral organisms did not necessarily mean infection by *Spirochaeta pallida*. It was stated that in an examination limited to the morphologic characteristics of organisms little weight could be placed on the distinguishing features on account of the close resemblance between the syphilitic and saprophytic spirochetes. Reference was made to the organisms demonstrated by

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1 Luria, R. Syphilitische und syphilogene Magenerkrankungen (Gastrolues), *Arch f Verdauungskr (supp)* **46** 1, 1929.

2 Singer, H. A., and Dyas, F. G. Syphilis of the Stomach with Special Reference to Certain Diagnostic Criteria, *Arch Int Med* **42** 718 (Nov.) 1928.

Pilot and Davis<sup>3</sup> in Levaditi preparations of lungs with abscess and gangrene, in which the spirochetes, although of oral origin, presented the typical appearance of *Spirochaeta pallida*. While the article by Dyas and myself was in press a report appeared by Welch<sup>4</sup> in which the syphilitic nature of the spirochetes pictured by McNee<sup>5</sup> was questioned and the opinion expressed that they might have been secondary invaders.

In writings on gastric syphilis up to 1928 no one, with the exception of Schmorl,<sup>6</sup> whose comment in 1907 has been entirely overlooked, apparently investigated the significance of spirochetes in syphilis of the stomach. It was presumably taken for granted that any spirochete present possessing the typical morphology was *Spirochaeta pallida*. As a matter of fact the statements of Dyas and myself to the contrary have seemed so heterodoxical that they have been entirely disregarded or looked on askance. O'Leary,<sup>7</sup> whose experience includes the study of eighty-nine cases of gastric syphilis, wrote with regard to the specificity of demonstrable spirochetes: "Singer and Dyas doubted that the organisms found by McNee were *Spirochaeta pallida*, and expressed the belief that they were Vincent's spirilla.<sup>8</sup> Hartwell, however, accepted McNee's observation as authentic." O'Leary, in making this statement, evidently inferred that we were incorrect in denying the specificity of McNee's organisms, for he continued to assert: "Waitlin reported that he has demonstrated the *Spirochaeta pallida* in eight cases of gastric syphilis in practically all of which operation was done because of a diagnosis of peptic ulcer. The incidence of the demonstration of *Spirochaeta pallida* in the gastric ulcer of the gummatous type no doubt will be higher in the hands of pathologists who become expert in its identification."

The question of the nature of the spirochetes demonstrated in lesions of the stomach is not only of scientific but also of practical importance. First with regard to diseases presenting the histologic characteristics of syphilis. The only case in which spirochetes interpreted as of the

3 Pilot, I, and Davis, D. J. Studies in Fusiform Bacilli and Spirochetes, *Arch Int Med* **34** 313 (Sept.) 1924. Pilot, I, Davis, D. J., and Shapiro, J. J. Studies on Fusiform Bacilli and Spirochetes, *Am Rev Tuberc* **8** 249 (Nov) 1923.

4 Welch, A. S. Diagnosis of Syphilis of the Stomach, *Am J Syph* **12** 325 (July) 1928.

5 McNee, J. W. Syphilis of the Stomach, *Quart J Med* **15** 215, 1921.

6 Schmorl, in discussion of Jores, L. Demonstration von gummoser Magensyphilis, *Verhandl d deutsch path Gesellsch* **11** 319, 1907.

7 O'Leary, P. A. Gastric Syphilis. Data Accumulated from 89 Cases, *Am J Surg* **11** 286 (Feb) 1931.

8 We<sup>2</sup> used the term Vincent in a broad sense to refer to the various saprophytic organisms of the oral origin.

pallida type were demonstrated in a stomach histologically syphilitic is, as will be submitted later, that of McNee<sup>5</sup> If spirochetes occurring in such numbers as pictured by McNee are of the pallida type, the organism should be demonstrable in at least a fairly high percentage of other syphilitic stomachs. In this event, the presence or absence of spirochetes should decide the diagnosis. If the demonstration of the organism is the basic criterion, none of the many other cases reported as gastric syphilis can be accepted. The conclusion which follows is that syphilis of the stomach is an exceedingly rare disease. The corollary to this would be that numerous patients are receiving antisymphilitic treatment unnecessarily. On the other hand, if the spirochetes portrayed by McNee can be shown to be nonsymphilitic, it is reasonable to assume that the absence of spirochetes does not militate against the diagnosis and that the therapeutic response should continue to constitute the chief diagnostic criterion and to indicate the treatment required. The second type of gastric lesion in which spirochetes considered syphilitic were found is the chronic peptic ulcer. The only author, as will be shown later, who has demonstrated spirochetes identified as syphilitic in what were apparently peptic ulcers is Warthin<sup>9</sup>. If Warthin's bacterioscopic interpretation in these cases, which would otherwise have been considered simple ulcer is correct, it can be assumed that a fair proportion of so-called peptic ulcers are syphilitic. It would also indicate that an examination limited to the anatomic features of a lesion, even though it showed typical chronic round ulcer, is insufficient as a basis for diagnosis, also that Levaditi preparations are indispensable. If, on the other hand, Warthin's spirochetes can be shown to be nonsymphilitic, it would follow that the cases of peptic ulcer ascribed by many to syphilis are probably nonsymphilitic and do not indicate antisymphilitic therapy.

In reviewing the literature, one is struck by the paucity of material on the subject of the significance of spirochetes in the stomach. However, the available reports are quite conclusive. Schmorl,<sup>6</sup> in 1907, pointed out that differentiation of syphilitic spirochetes from other, similar organisms in silver preparations was often impossible. He deplored the fact that the brilliant discovery of Schaudinn advanced the pathologic knowledge of syphilis only slightly, for in questionable cases, particularly, either the demonstration of the spirochete was unsuccessful or, when present, the pallida could not be distinguished readily from other types. The presence of spirochetes in the stomachs of nonsymphilitic subjects was clearly demonstrated in 1908 by

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<sup>9</sup> Warthin, A. S. Syphilis of the Smaller Arteries, New York M. J. **115** 69 (Jan 18) 1922

Simmonds<sup>10</sup> He found in degenerating carcinomas spiral organisms which he stated had their origin in the flora of the mouth He asserted that the spirochetes were found not alone on the surface but also in the tissues He concluded that their presence was of significance in that they might be confounded with those of syphilis In the discussion which followed, Fraenkel<sup>11</sup> stated that many of the spirochetes portrayed by Simmonds could not be differentiated from those causing syphilis

The early observations of Schmoil, Simmonds and Fraenkel, to the effect that spirochetes originating in the mouth were present in the gastric wall and were practically indistinguishable from the specific organism of syphilis, have received ample substantiation With regard to incidence, the frequent occurrence in the lumen of the stomach of spirochetes derived from the oral cavity has been firmly established by Luger and Newberger,<sup>12</sup> especially in connection with carcinoma In sixteen cases of malignant gastric conditions studied by them the aspirated contents of the stomach after fasting showed in eleven a more or less rich spirochetal flora Direct smears from the surface of five gastric carcinomas showed enormous numbers of spirochetes in all With regard to the morphologic differentiation, bacteriologists are agreed that the resemblance between specific and certain saprophytic spirochetes is an extremely close one Park and Williams,<sup>13</sup> whose recent text can be considered authoritative, indicated that the differences between *Spirochaeta pallida* and for instance *Treponema dentium* are merely relative and not absolute Erich Hoffman,<sup>14</sup> with whom Schaudinn discovered *Spirochaeta pallida* in 1905, expressed the opinion that a differentiation of the *pallida* type from morphologically similar types (which he offered to designate as *Spirochaeta pseudopallida*) demands further study

The differences between syphilitic and saprophytic spirochetes in stained smears and hanging drops are even less apparent in histologic preparations The lack of detail of *Spirochaeta pallida* in tissues impregnated with silver is quite apparent when compared with dark-

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10 Simmonds Ueber Spirochäten Befunde in Karzinomen, München med Wchnschr 55 1103, 1908

11 Fraenkel, E, in discussion of Simmonds (footnote 10)

12 Luger, A, and Newberger, H Ueber Spirochäten-Befunde im Magensaft bei Carcinoma ventriculi, Wien med Wchnschr 70 1254 (July 3) 1920

13 Park, W H, Williams, A W, and Krumwiede, C Pathogenic Microorganisms, ed 8, Philadelphia, Lea & Febiger, 1924, p 529

14 Hoffman, E, and Hofmann, E Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol 15, pt 1, p 87

field preparations and smears (Noguchi<sup>15</sup>) Pilot and Davis, who have made a comprehensive study of spirochetes of the mouth in pulmonary abscess and gangrene, consider the differentiation between saprophytic spirochetes and *Spirochaeta pallida* in silver preparations very difficult and at times impossible Comparison between spirochetes in Levaditi stains of nonsyphilitic lesions of the stomach and known *Spirochaeta pallida* lends substantiation to the views already expressed Figures 1 and 2 are photomicrographs from a necrotizing, ulcerating

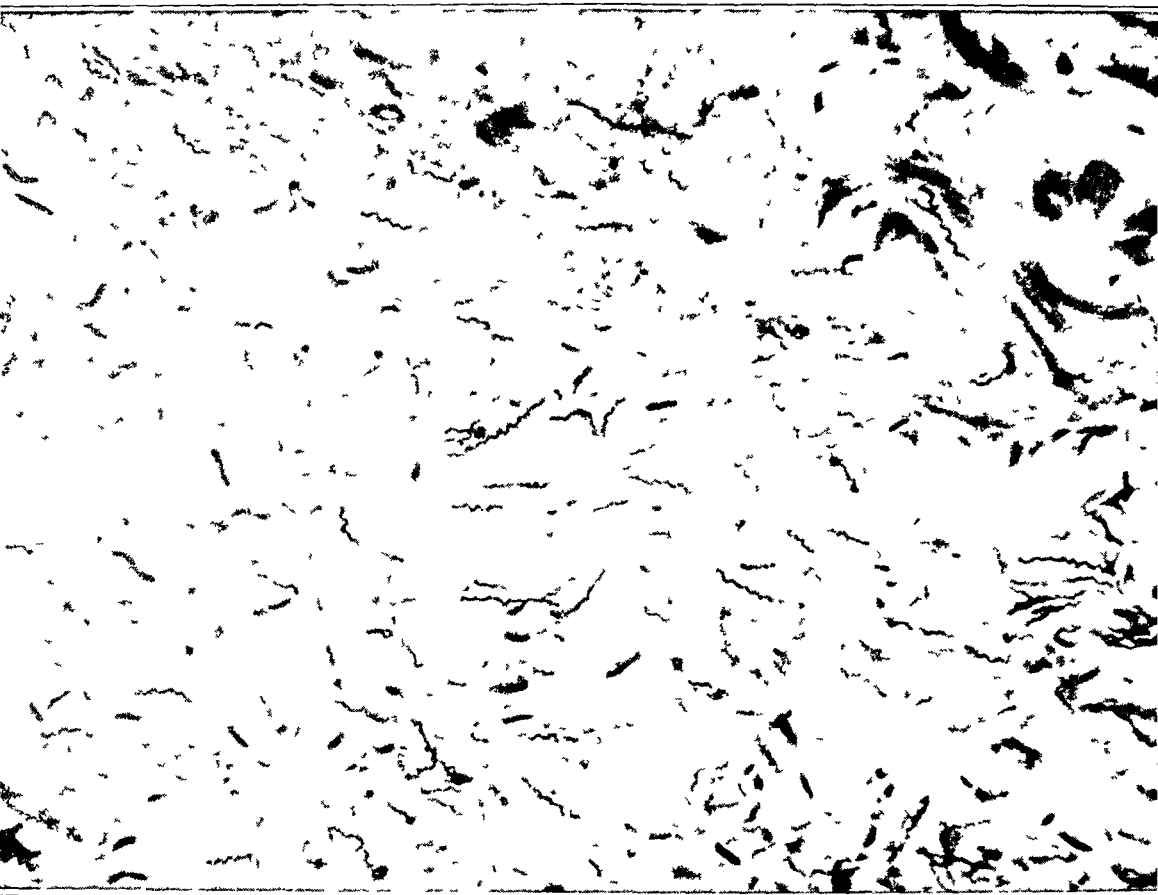


Fig 1—Levaditi preparation of a section taken from the superficial portion of a necrotizing, ulcerating carcinoma of the stomach encountered at autopsy No indication of syphilis was found during life or at postmortem examination The spirochetes, which in many instances resemble *Spirochaeta pallida*, are saprophytic and are derived from the mouth Fusiform bacilli are found in association with the spirochetes This photomicrograph has not been retouched

carcinoma of the stomach obtained at autopsy The argentaffine organisms present are almost unquestionably of oral origin, for there was no clinical, serologic or anatomic evidence of a syphilitic infection

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15 Noguchi, H The Spirochetes, in Jordan, E O, and Falk, I S The Newer Knowledge of Bacteriology and Immunology, Chicago, University of Chicago Press, 1928, p 452

The resemblance of the oral spirochetes in nonspecific ulcerating lesions of the stomach to *Spirochaeta pallida* is apparent in these representative illustrations

In spite of the large number of cases of syphilis of the stomach which have been reported, only a few contain mention of the presence of spirochetes<sup>16</sup> Even the large series of ninety-three cases recorded by Eusterman<sup>17</sup> does not include a single one in which the spirochete was found Reference is made particularly by foreign authors to several articles in English dealing with spirochetes, but most of these reports are misquoted or misinterpreted Boas<sup>18</sup> mentioned Wile and Allbutt, and Luria<sup>1</sup> referred to the latter two and also to LeWald as having found *Spirochaeta pallida* in the tissues Investigation of the original articles indicates that Wile<sup>19</sup> simply made reference to a case of Waithin's, whereas Allbutt<sup>20</sup> and LeWald<sup>21</sup> described McNee's case Several writers, both foreign and native, have referred to Welch's<sup>4</sup> case as one in which the *Spirochaeta pallida* was demonstrated It is true that Welch stated "In one of many blocks we found spiral bodies characteristic of *Treponema pallidum* The preparation was passed on by several competent men, who could give no reason why the bodies seen were not *Treponema pallidum*" His object was to emphasize the difficulty in recognizing the causative organism of syphilis, for in the next sentence he wrote "Under a high-powered microscope, Dr H R Wahl, Professor of Pathology at the University of Kansas, showed that one of the most characteristic bodies was part of the so-called elastic membrane of a blood vessel" The only authors so far as has been ascertained, who have succeeded in identifying in gastric lesions, spirochetes which were considered syphilitic are McNee and Waithin The correctness of the morphologic diagnosis of the organisms demonstrated by these two writers has hardly been brought into question

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16 This statement and similar ones in the article refer solely to cases of gastric syphilis of clinical importance, and exclude the instances of congenital syphilis in the new-born

17 Eusterman, G B Gastric Syphilis, Observations Based on 93 Cases, *J A M A* **96** 173 (Jan 17) 1931

18 Boas, K Syphlogene Erkrankungen des Magens im Lichte moderner Forschungsergebnisse, *Zentralbl f Haut- u Geschlechtskr* **13** 1, 1924

19 Wile, U J Visceral Syphilis Syphilis of the Stomach, *Arch Dermat & Syph* **1** 543 (May) 1920, Visceral Syphilis Syphilis of the Intestine, *ibid* **3** 372 (April) 1921

20 Allbutt, T C Visceral Syphilis, Especially of the Central Nervous System and Cardiovascular System, *Brit M J* **2** 177 (Aug 6) 1921

21 LeWald, L T Leather-Bottle Stomach (Linitis Plastica), *Am J Roentgenol* **8** 163 (April) 1921



The doubt previously expressed regarding the syphilitic nature of the spirochetes in cases of acquired gastric syphilis having been overlooked or the basis for question considered inadequate, it appears desirable to analyze the facts given in connection with each report. The classic example of *Spirochaeta pallida* in a syphilitic stomach is that of McNee<sup>5</sup>. The accompanying photomicrograph (fig. 3) illustrates why it has met with general acceptance, for at first glance the picture is typical of the spirochetes of syphilis. However, there are several reasons for assuming that the organisms are derived from the oral flora. In the first place, in tertiary lesions of acquired syphilis a paucity of organisms is characteristic. The discovery of an occasional organism generally requires a painstaking, laborious search. The presence of many spirochetes is typical of a nonsyphilitic infection. In McNee's case in a single microscopic field (oil immersion) at least eighteen distinct spirochetes are represented. Furthermore, in an infection due to syphilis the spirochetes are unassociated with any other organisms. In nonsyphilitic lesions, on the other hand, in which saprophytic spirochetes invade the tissues, other micro-organisms, especially fusiform bacilli, are found in combination. The spirochetes, however, tend to migrate beyond the bacilli and to occupy an advanced zone (see Pilot and Davis<sup>3</sup>). McNee's observations answer to the latter description, for he wrote "Near the free surface the spirochetes in the necrotic surface layer were mixed with other organisms, but in the deeper granulation tissue close to the muscular coat they were unaccompanied by any other demonstrable organism." Another important consideration is the type of tissue in which the spirochetes were found. As pointed out, saprophytic spirochetes of the mouth, which for all practical purposes are morphologically indistinguishable from the *pallida* type, are found in degenerated tissue of the gastro-intestinal tract with regularity. In order to be valid, *Spirochaetae pallidae* should be observed more or less remotely from necrotic areas. However, the block containing the spirochetes was taken from an area manifestly necrotic, judging from the photograph accompanying the article and also from McNee's own description. Finally, it should be taken into account also that of eight blocks of tissue from known situations which were stained according to Levaditi's method only one revealed spirochetes. Syphilis would hardly be expected to show *Spirochaetae pallidae* localized to only one area of a granulomatous infiltrate of hematogenous origin. However, if one assumes that the organisms found represented secondary invaders and were not primarily responsible for the extensive lesion, the explanation becomes apparent.

McNee is most frequently cited in connection with syphilis of the stomach and spirochetes because of his convincing illustration rather

than the number of cases, for he reported but one instance Warthin,<sup>22</sup> who has observed eight cases, is mentioned less frequently probably because he has published the details of none and, so far as can be ascertained, has not reproduced by photograph the spirochetes observed. In a paper<sup>9</sup> dealing with syphilis of the smaller arteries he made the statement that specific inflammation of the gastric and duodenal arterial branches is an undoubted factor in the production of peptic ulcer. He wrote "We have had three cases of syphilitic peptic ulcer of the stomach. In one of these, from Dr. Cabot's service, the syphilitic vascular disease was very pronounced, and the neighboring lymph nodes showed active syphilitic lesions. Spirochetes were found in numbers, both in the perivascular infiltrations of the stomach wall and in the lymph nodes." This same case was referred to in a previous publication from the University of Michigan by Wile,<sup>19</sup> who recorded that the Wassermann reaction was negative. In a more recent paper by Warthin<sup>22</sup> dealing with the relationship of gastric carcinoma and ulcer he merely mentioned the fact that he had had "eight cases of ulcer of the stomach that are definitely shown to be syphilis." These eight cases are referred to by both O'Leary<sup>7</sup> and Eusterman<sup>17</sup> as proved cases of peptic ulcer of syphilitic origin.

The weight of Warthin's authority on the subject of syphilis and especially on that phase dealing with spirochetes tends to lead many to accept his statements without hesitation. The syphilitic origin of peptic ulcer, however, is seriously questioned by most authorities on gastric syphilis. Konjetzny,<sup>23</sup> whose chapter on syphilis of the stomach in Henke's and Lubarsch's system of pathology probably represents the current opinion, denies the existence of peptic ulcer due to syphilis. He corroborates the view of E. Fraenkel<sup>24</sup> and Lubarsch<sup>25</sup> that the vascular changes described in connection with these lesions and ascribed to syphilis are not specific but can be found in simple ulcers. In the anatomic study of established cases of syphilis of the stomach, one gains the impression that the syphilitic infiltration is primary and that ulceration is secondary. The striking differences between peptic ulceration, which is primary, and syphilitic ulceration, which appears to be secondary to an infiltrate, is well illustrated in an article by

22 Warthin, A. S. The Relation of Cancer of the Stomach to Ulcer. Proc. Inter-State Post-Grad. M. Assemb., North America, Oct. 17-21, 1927, p. 162.

23 Konjetzny, G. E. Die Entzündung des Magens, in Henke, F., and Lubarsch, O. Handbuch der speziellen pathologischen Anatomie und Histologie. Berlin, Julius Springer, 1928, vol. 7, pt. 2, p. 1015.

24 Fraenkel, E. Zur Lehre von der erworbenen Magen-Darmsyphilis, Virchows Arch. f. path. Anat. **155**: 507, 1899.

25 Lubarsch, O., quoted by Baumecker, H. Die klinische Diagnose der hypertrophischen Magenlues, Med. Klin. **26**: 1557 (Oct. 17) 1930.

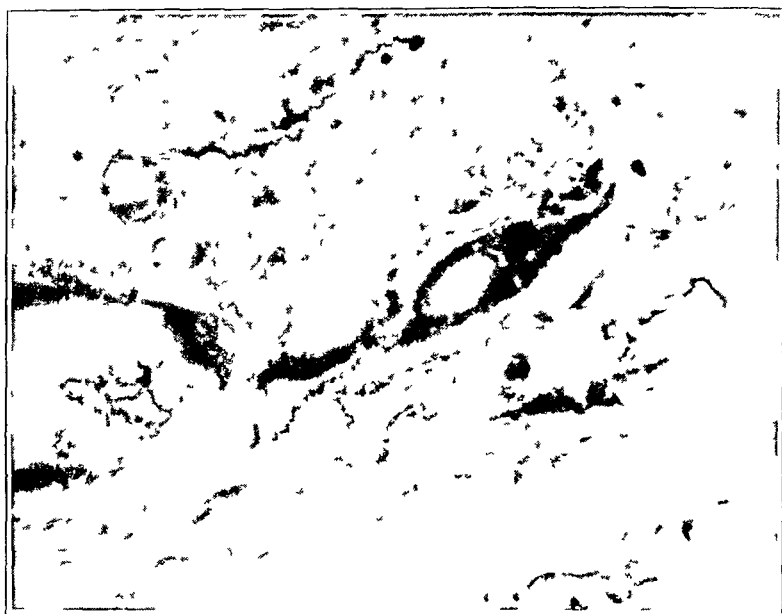


Fig 2—This preparation is from the same section as that in figure 1 but somewhat deeper. The spirochetes have migrated beyond the necrotic surface layer in advance of the fusiform bacilli. This photomicrograph has not been retouched.



Fig 3—McNee's illustration of a retouched photomicrograph of a section from a case of gastric syphilis (see text), stain by Levaditi's method (reproduced from *British Journal of Surgery* [supp.] **14** 100, 1927)

Brams<sup>26</sup> The occurrence of spirochetes in the wall of an ulcer has little significance per se. The presence of spirochetes in limited numbers was demonstrated in the gastric contents of patients with ulcer by Luger and Newberger<sup>22</sup>. Spirochetes were recovered in smears from the floor of peptic ulcers by Pewny<sup>27</sup> and identified in the walls by Lehner<sup>28</sup>. These were indubitably saprophytic spirochetes and since, as contended, spirochetes from the mouth cannot be readily distinguished morphologically from *Spirochaetae pallidae*, it is difficult to accept Warthin's assumption as proved. It is a noteworthy fact that in the only case of Warthin's in which any data were offered, the Wassermann reaction was found negative. When a lesion containing demonstrable spirochetes "in numbers" exists, a negative Wassermann reaction it seems, would require investigation of the nature of the organisms present.

Some time ago I submitted for publication in one of the recognized journals an article on syphilis of the stomach which included two cases with classic anatomic findings. The manuscript was returned by the editor with the statement that in his opinion the frequent publication of "probable" cases did not greatly advance the subject. He wrote that he would be glad to accept any reports in which spirochetes had been demonstrated, and specified that a certain prominent authority on syphilis be persuaded to aid in the search. Following this suggestion when the next case of syphilis of the stomach presented itself, I mailed the material to the investigator recommended, who kindly consented to examine it. He reported that the histologic appearance was characteristic of syphilis and that *Spirochaetae pallidae* were demonstrable in the section, the slide containing the organisms, with their location indicated, was returned to me. For reasons to be given later, the investigator's diagnosis was not accepted as final, since the spirochetes present were morphologically identical with those seen in nonsyphilitic stomachs. The essential available facts in connection with the case are here submitted for analysis.

#### REPORT OF A CASE

*History*—A colored man, Oliver C., 22 years of age, entered the Cook County Hospital on Jan. 11, 1930, with the tentative diagnosis of obstructive ulcer. He related that he was first troubled nine months before entrance, when he noted a sense of epigastric fulness following meals. This at times was associated with

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26 Brams, W. A. Ueber das Ulcus syphiliticum multiforme ventriculi, *Arch f. Verdauungskr.* **27** 375, 1921.

27 Pewny, W. Spirochäten bei Ulcus ventriculi, *Wien. med. Wchnschr.* **70** 1925 (Nov. 6) 1920.

28 Lehner. Ueber das Vorkommen von Spirillen im menschlichen Magen, *Wien. klin. Wchnschr.* **40** 957, 1927.

heart-burn In a short while, actual pain supervened, occurring as a rule but once a day The pain was epigastric and cramplike

The patient's symptoms gradually increased in intensity until one month previous to admission, when a decided aggravation took place The epigastric pain now occurred following every meal, being noted from fifteen minutes to one hour after eating In the last two weeks of the illness the pain radiated around the right side to the middle of the back Vomiting appeared almost simultaneously with the occurrence of postprandial pain The vomiting became more and more frequent, and at the end of the two weeks the patient was unable to eat without subsequent emesis The vomitus had the appearance of coffee-grounds

The remainder of the history yielded only a few pertinent facts The stools during the last few days of the patient's illness were tarry The appetite was poor During the month prior to entrance the patient estimated that he lost 25 pounds (11.3 Kg) The loss of strength was quite profound The patient acknowledged two gonorrheal infections, but denied syphilis The family history suggested nothing indicative of syphilis

*Examination*—The patient appeared listless and showed evidence of loss of weight and pallor A tumor mass was not palpated From the laboratory standpoint it was determined that the first stool was tarry, but that the amount of blood rapidly decreased until merely occult blood remained The material vomited the day of admission contained altered blood A subsequent Ewald test meal yielded 195 cc of poorly digested contents with 12 degrees free and 52 degrees combined acidity The Wassermann and Kahn tests were 4 plus A roentgenogram on January 22 was read by Dr C H Warfield as follows There was an irregular, annular constriction of the middle of the pars pylorica, which produced only moderate obstruction Bordering on the lesser curvature, just proximal to the cylindric narrowing, there was a filling defect about which the rugous markings were lost Carcinoma and syphilis were to be considered

*Course*—When the patient entered the ward, treatment for bleeding peptic ulcer was instituted The positive report on the routine Wassermann test led to the suspicion of syphilis of the stomach, and antisyphilitic therapy (neoarsphenamine) was instituted two days after admission Although the vomiting subsided to a great extent, the patient continued to complain of pain after eating and on that account greatly curtailed his food intake The attending physician to whom the patient was assigned considered the response to the two and a half weeks of antisyphilitic treatment too poor to support the diagnosis of syphilis of the stomach He considered carcinoma more likely, and therefore recommended surgical intervention

*Operation*—Laparotomy undertaken on January 30 disclosed the pyloric portion of the stomach to be infiltrated by a relatively soft, elastic mass, which lacked the firmness and circumscription of a tumor The encroachment on the lumen was only moderate The perigastric glands were only slightly enlarged, pink and soft There were no evidences of active or healed gummas detected in the examination of the liver Because of the fear of carcinoma, gastric resection was performed The patient withstood the immediate effects of the operation quite well Beginning, however, with the third postoperative day his condition became worse It was soon apparent that peritonitis had supervened He died on February 5, six days after operation

The postmortem examination was made by Dr R H Jaffe, whose anatomic diagnosis reads diffuse fibrinopurulent peritonitis, recent gastric resection and posterior gastro-entero-anastomosis with suppuration about the sutures, bilateral serofibrinous pleuritis with slight compression of the lower lobes, fatty

degeneration of the liver, parenchymatous degeneration of the myocardium and kidneys, infectious softening of the spleen, focal syphilitic aortitis in the region of the arch and above the aortic valve, an encapsulated tuberculous lesion in the left lower pulmonary lobe, circumscribed pyelonephritic atrophy of the left kidney, marked emaciation

*Surgical Specimen*—Gross Description The unopened resected distal third of the stomach measured 72 and 11.5 cm along the lesser and greater curvatures respectively. The specimen had roughly the shape of a dumbbell, owing to slight narrowing of its midportion over an area which measured 3 cm. Corresponding more or less to the extent of the cylindric constriction the serosa appeared white and fibrous. The differences between the apparently normal and abnormal portions, as determined by palpation, were far from striking. The narrowed area was felt to be thickened, but was only slightly increased in consistency and relatively supple. The pliability was in sharp contrast to the character of the infiltrate encountered in carcinoma with a similar distribution. The thickened area passed insensibly into the adjoining normal tissue. The opened specimen demonstrated that the moderate narrowing of the prepyloric region noted in the external examination was exaggerated by encroachment on the lumen of the thickened gastric wall. The area of maximum thickening, which was about the size of a silver dollar, was located on the anterior wall near the lesser curvature. From here the thickness of the wall diminished in passing radially. At the summit of the area of increased thickness there was a superficial ulcer with irregular, serpiginous margins. The maximum and minimum diameters measured 4.5 and 3.3 cm respectively. The edges of the ulcer were neither raised nor undermined. The floor was covered with a grayish-brown, lardaceous, slightly adherent membrane. The remainder of the gastric lining, except for a little thickening, was unchanged. A cross-section of the wall in the region of the ulcer showed that the base of the latter was considerably above the level of the normal mucous membrane. The individual coats in the region of maximum thickness were adherent, but could be readily identified. The submucosa was represented by a relatively narrow layer of white, homogeneous tissue from which septums extended into the muscularis propria in lattice-like arrangement. The serous coat was greatly thickened, constituting from one-half to two-thirds the thickness of the gastric wall. It was composed of homogeneous, white tissue of elastic consistency.

*Microscopic Description* The most pronounced changes were observed in sections taken in and about the region of the serpiginous ulcer which corresponded to the area of maximum thickness of the gastric wall. In passing centrifugally the histologic alterations became less and less prominent, leading gradually to relatively normal-appearing structures. The following description of a section taken from a margin of the ulcer to include the entire thickness of the stomach is quite representative (fig. 4).

Under very low magnification, the wall at one edge of the section was found to be increased to about three times the normal thickness, gradually tapering down in passing to the opposite end, to approach the thickness of the average stomach. In the thin portion the mucosa presented a relatively normal appearance except for an increased cellularity of the tunica propria. In approaching the margin of the ulcer the round and plasma cells in the interglandular tissue became more and more numerous and associated with an unusual number of prominent lymphoid follicles. As the wall became thicker the mucosa was displaced obliquely upward, until a point was reached at which the gastric lining was absent. The floor of the defect, however, continued for a short distance to pass obliquely upward, so that at no point was the normal mucosa above the level of the base of the ulcer.

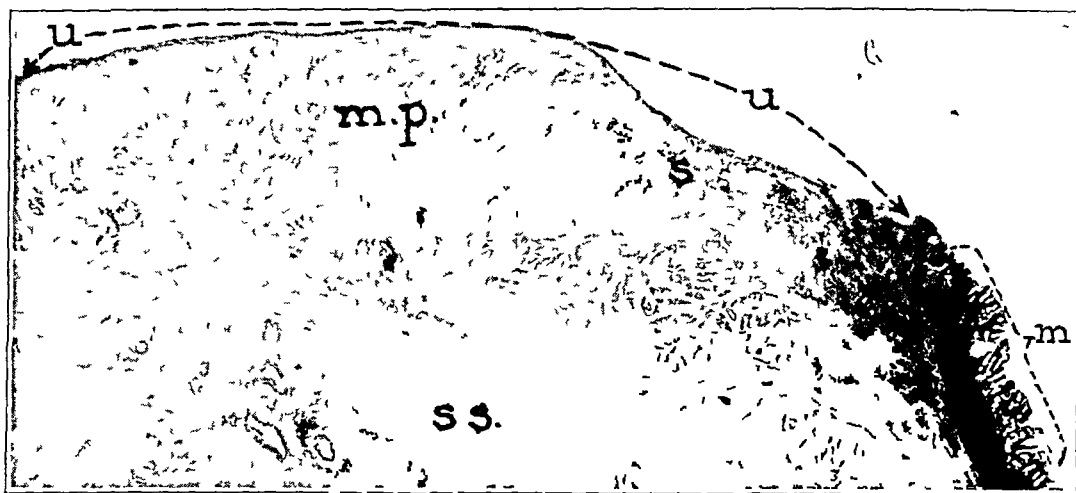


Fig 4—A cross-section of the wall of the stomach at the junction of the intact mucosa (*m*) and margin of the ulcer (*u*). At the periphery of the ulcer the floor is formed by submucosa (*s*), toward the center it is formed by muscularis propria (*m.p.*). The thickening of the gastric wall is due mainly to an increase in the subserosa (*s.s.*). The base of the ulcer is at a higher level than the intact mucosa. Obtained from the same specimen as the tissue shown in figure 5 (see report of case)



Fig 5—The material from which these photomicrographs were made was prepared and examined by an authority on the subject who made the diagnosis of syphilis from the histology and also from the morphology of the spirochetes demonstrated (see report of case). The three organisms pictured were found in separate fields. The spirochete which bore the closest resemblance to *Spirochaeta pallida* is shown in *A*. Most of the spirochetes encountered were of the types illustrated in *B* and *C*. The spirochete in *B* was actually twice as long as the photomicrograph indicates, since only one-half is included in the focus.

The muscularis mucosa showed moderate thickening due to an increase in muscle elements and infiltrations of round and plasma cells. It became lost after reaching the margin of the ulcer. The submucosa was also the seat of thickening due mainly to the presence of an increased and edematous connective tissue. Focal accumulations of cells, mainly round and to a lesser degree plasma cells, were scattered throughout this layer. In places these cells assumed a perivascular arrangement, but did not invade the vessel walls. In fact, the changes in the blood vessels themselves were exceedingly mild. In approaching the margin of the ulcer the cellular infiltrates became more numerous and larger, finally coalescing to form a solid wall. The submucosa, soon after entering the ulcer, constituted its floor and within a short space became destroyed.

The muscularis propria was invaded by connective tissue septums, which appeared to arise from the overlying and underlying layers. There were also accumulations of cells similar to those seen in the submucosa. The changes were most prominent in the ulcerated region, especially in that part in which the submucous layer was absent and the muscularis formed the base of the ulcer. Here the muscle bundles were infiltrated and the individual fibers appeared atrophic and stained poorly.

The serosa exhibited a prodigious thickening, constituting approximately one half of the total thickness of the gastric wall. The maximum increase was found underlying the area of ulceration. The histologic changes were similar to those found in the submucosa except that the fibrous tissue in the serosa was less dense.

The ulcer had a uniform base which resembled closely that of a peptic ulcer. The surface of the defect was covered by a dark granular debris beneath which there was a zone of fibrinoid necrosis. Subjacent to this layer there was a young granulation tissue densely infiltrated by numerous round cells and lesser numbers of plasma leukocytic and histiocytic cells. Underlying the layer of young granulation tissue was one which was poorer in cells and richer in collagen fibers. Successively the mucosa, muscularis mucosae, submucosa and superficial portions of the muscularis propria became destroyed. In no area did the base of the ulcer extend beyond the muscular coat.

*Bacteriologic and Biologic Examination*—Macerated preparations of gastric wall taken from the region of maximum involvement immediately after operation and examined with dark-field illumination failed to demonstrate the presence of *Spirochaeta pallida*. Inoculation of a saline suspension of the macerated tissue into the testicles of rabbits failed to produce signs of a scrotal chancre. Material taken from the same region which included the ulcer was fixed in a diluted solution of formaldehyde U S P (1:10). Some blocks were retained and examined for tubercle bacilli, with negative results. Other blocks, together with pertinent data, were sent to the investigator previously referred to, with the request that he examine the tissue for *Spirochaetae pallidae*. His report read: "Positive for *Spirochaetae pallidae*. Typical spirochetes are rare. Atypical forms are more numerous, but are still uncommon. Granular and ring stages are common. The typical spirochetes are found only in the zone bordering the necrotic tissue of the ulcer. Histology characteristic of syphilis."

#### COMMENT

The location of those spirochetes considered most typical by the authority consulted was indicated by a ring of ink on a slide which he returned to me. The organism in this preparation which, in the opinion of the disinterested observers (Dis R H Jaffé and I Pilot),



resembled classic *Spirochaeta pallida* most closely is pictured in figure 5A. The more frequent type encountered is illustrated in figure 5B and C. Neither I nor my associates in pathology and bacteriology could distinguish the spirochetes found within the circle from those seen in necrotic lesions of nonsyphilitic origin. One is led to believe that the spirochetes found in the section and considered of the *pallida* type by the investigator were more probably saprophytic than pathogenic. As stated by him in his letter and indicated by him in the section, the "typical" spirochetes were found only in the zone bordering the necrotic tissue of the ulcer. In the foregoing description it was pointed out that saprophytic spirochetes morphologically resembling the syphilitic type are frequently located in and border on necrotic lesions of the stomach. It was stated, furthermore, that these spirochetes were generally accompanied by fusiform bacilli together with other microorganisms. In the consultant's section fusiform bacilli could be found with relative ease and, in fact, served as a guide in the search for spirochetes. By far most of the spirochetes found were of the type illustrated in figure 5B and C and were distinctly different from the classic ones, as indicated by the consultant's statement, viz. "Typical spirochetes are rare. Atypical forms are more numerous but are still uncommon." These "atypical" *Spirochaetae pallidae* appear morphologically to be identical with certain varieties of mouth spirochetes found in nonspecific necrosis of gastric as well as other tissues.

Assuming the consultant's bacteriologic diagnosis of *Spirochaeta pallida* to be doubtful, the question naturally arises as to the evidence on which the diagnosis of gastric syphilis is founded. The histologic picture, although compatible with the diagnosis of syphilis, is not distinctive of this disease. In fact, the changes in this case are less characteristic of syphilis than those in any of the other cases that I have reported. In all previous instances which were studied microscopically the vascular changes were at least in a measure typical of syphilis. In the stomach herein described neither the arteries nor the veins were the seat of any noteworthy degree of inflammation. It is not unlikely that the antisyphilitic therapy modified to some extent the histology of the lesion. The diagnosis is based in this instance on collective evidence derived mainly from clinical data: the age of the patient (22 years), the progressive course, the hypochlorhydria, the roentgen observation of an irregular, annular deformity situated proximal to and not invading the pylorus, and the positive Wassermann reaction. Further support is adduced from the therapeutic response which, although not striking, was sufficient to conclude that the patient was greatly benefited by the antisyphilitic treatment. The gross description of the lesion is quite characteristic of syphilis. The typical features

include a relatively soft, indefinitely outlined infiltrate in the thickest portion of which is a superficial, seipiginous ulcer of irregular form. The absence of a noteworthy degree of lymphadenopathy and the lack of microscopic evidence of carcinoma are of negative value in the diagnosis. Finally the autptic demonstration of a syphilitic aortitis and no other disease or lesion to explain the gastric involvement lends additional support to the diagnosis.

It is thus seen that what might have been recorded as a case of "proved" gastric syphilis based on the demonstration of spirochetes was actually one of presumptive or perhaps questionable syphilis. The diagnosis rests on clinical, laboratory, therapeutic and macroscopic anatomic observations. The bacterioscopic and histologic examinations yielded nothing of positive value in arriving at the diagnosis. It is quite possible that the gastric involvement represented a nonsyphilitic granuloma in a syphilitic patient rather than a true syphilitic lesion. In either event from the clinical standpoint it would have been to the patient's advantage to have treated him on the supposition that he was suffering from a syphilitic disease of the stomach. Whatever the conclusions of the morbid anatomists may be the fact remains that clinically, patients who present the foregoing syndrome are best treated for gastric syphilis. Obviously, all precautions against mistaking carcinoma for syphilis must be observed. In doubtful cases operation is indicated. The differentiation can generally be made with relative ease, particularly with the aid of a frozen section, which is of value in excluding malignancy.

NOTE—Since this article was submitted for publication a report appeared by Harris and Morgan dealing with the demonstration of spirochetes from a syphilitic stomach by means of inoculation of animals.<sup>29</sup> The description of the gross and histologic characteristics of the resected specimen is too brief to admit of any opinion. The spiral forms pictured in a photomicrograph of a section stained by the Levaditi method do not resemble spirochetes and, as the authors themselves state, "could not be identified as *Spirochaeta pallida*." However, inoculation of a tissue suspension of material from the gastric lesion and also from a regional lymph gland into four rabbits resulted in testicular syphilomas in two and a scrotal chancre in one of these two. Dark-field examination of scrapings from the lesions revealed "*Spirochaeta pallida* in countless numbers and typical in form." Repeated transfer of the spirochetes to other rabbits resulted, according to the authors, in the production of characteristic local and metastatic lesions of experimental syphilis.

In a discussion of gastric syphilis before the Section on Gastro-Enterology at the eighty-first annual session of the American Medical Association in June, 1930, I emphasized the difficulty in differentiating certain types of spirochetes in Levaditi preparations. I further stated "A hanging drop preparation is more favorable for identification of spirochetes of syphilis, and rabbit inoculation, when positive,

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29 Harris, S., and Morgan, H. J. The Isolation of *Spirochaeta Pallida* from the Lesion of Gastric Syphilis, J. A. M. A. 99 1405 (Oct 22) 1932

most conclusive" <sup>30</sup> It should be borne in mind, however, that although animal inoculation offers more conclusive evidence than other methods of differentiating spirochetes, the experimental lesions and the organisms obtained therefrom are by no means unmistakable. Rabbit spirochetosis, a spontaneous venereal disease of rabbits, constitutes a potential source of error in that the etiologic organism, *Spirochaeta cuniculi*, is practically indistinguishable from *Spirochaeta pallida* (Noguchi <sup>31</sup>). A number of reliable distinguishing features, clinical, serologic and anatomic, between rabbit spirochetosis and experimental syphilis are recognized by many authorities, nevertheless dissenting views are not lacking <sup>32</sup>.

The observation by Neumann <sup>33</sup> of the spontaneous appearance in a rabbit of spirochetes of the *pallida* type adds further to the doubt expressed by several authors regarding the value of the rabbit in the recognition of syphilis in human beings. Of particular interest is the report of Worms, <sup>34</sup> who inoculated a rabbit with material from the mouth of a nonsyphilitic man. The rabbit developed lesions which contained spirochetes indistinguishable from *Spirochaeta pallida*. Attempts to inoculate other rabbits from the experimental lesions were uniformly successful. On account of the possibility of error in connection with animal inoculation all available evidence should be gathered and recorded in order to establish proof when the diagnosis of syphilis of the stomach is made. Although the work of Harris and Morgan is quite convincing, confirmation by others is nevertheless desirable.

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30 Singer, H. A., in Discussion on Gastric Syphilis, J. A. M. A. **96** 186 (Jan 17) 1931.

31 Noguchi, <sup>15</sup> p. 478.

32 Sobernheim, G. Syphilisspirochete, in Kolle, W., Kraus, R., and Uhlenhuth, P. Handbuch der pathogenen Mikroorganismen, ed. 3, Jena, Gustav Fischer, 1930, vol. 7, pt. 1, p. 107.

33 Neumann, F. Ueber das spontane auftreten von Spirochäten des *pallida*-typs bei einem Nichtsyphilitischen, isolierten Kaninchen, Klin. Wchnschr. **2** 256 (Feb. 5) 1923.

34 Worms, W. Bemerkungen zur Arbeit von Dr. F. Neumann, Klin. Wchnschr. **2** 836 (April 30) 1923.

# EXPERIMENTAL CORONARY OCCLUSION

INADEQUACY OF THE THREE CONVENTIONAL LEADS FOR RECORDING  
CHARACTERISTIC ACTION CURRENT CHANGES IN CERTAIN  
SECTIONS OF THE MYOCARDIUM, AN ELEC-  
TROCARDIOGRAPHIC STUDY

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It has been known since the original observations of Smith<sup>1</sup> and Pardee<sup>2</sup> that in some instances an acute myocardial infarction causes a characteristic change in the ventricular complex of the electrocardiogram. In certain other instances of infarction, however, definite electrocardiographic evidence of the presence of the infarct has not been obtained. The reason for this apparent limitation of the electrocardiographic method in both clinical and experimental studies has not been clearly understood.<sup>3</sup> The observations to be reported here have a bearing on this problem.

## EXPERIMENTS

In our earlier studies the following technic was employed. Dogs were subjected to iso-amyl-ethyl-barbituric acid anesthesia. A cannula was placed in the trachea and connected with the ordinary respiratory pump. The chest was opened along the sternum. The pericardium was opened longitudinally. Its edges were sewed to the lateral wall of the chest, making a hammock to hold the heart in position. The coronary arteries were dissected free, threads were passed beneath

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From the Edward B. Robinette Foundation, Hospital of the University of Pennsylvania

1 Smith, F. M. The Ligation of Coronary Arteries with Electrocardiographic Study, *Arch. Int. Med.* **22**: 8 (July) 1918

2 Pardee, H. E. B. An Electrocardiographic Sign of Coronary Artery Obstruction, *Arch. Int. Med.* **26**: 244 (Aug.) 1920

3 (a) Wood, F. C., and Wolfert, C. C. Angina Pectoris. The Clinical and Electrocardiographic Phenomena of the Attack and Their Comparison with the Effects of Experimental Temporary Coronary Occlusion, *Arch. Int. Med.* **47**: 339 (March) 1931. (b) Feil, H. S., Katz, L. N., Moore, R. A., and Scott, R. W. The Electrocardiographic Changes in Myocardial Ischemia, *Am. Heart J.* **6**: 522 (April) 1931

them to facilitate subsequent manipulations. Coronary occlusion was produced by means of bulldog clamps. Electrocardiograms were taken with the three conventional limb leads. The accompanying table shows the number of animals employed, and indicates the numbers of the various experiments carried out.

We found,<sup>3a</sup> as did other observers,<sup>3b</sup> that occlusion of the anterior descending branch of the left coronary artery produced little or no change in the electrocardiogram, despite a marked alteration of the appearance and action of the heart. Obstruction of the right coronary artery likewise caused practically no change in the ventricular complex. However, when the posterior circumflex branch of the left coronary artery or one of its large descending branches was occluded, a definite

### *Summary of Experimental Procedures*

	Series 1*	Series 2†	Series 3‡	Series 4§
Number of dogs used	10	6	10	8
Number of experiments in which the left anterior descending artery was clamped	34	15	31	29
Branch of left anterior descending artery clamped	6	15	1	4
Right coronary artery clamped	24	9	20	10
Left posterior circumflex artery clamped	48	10	6	20
Branch of left posterior circumflex artery clamped	20		2	6
Vena cava alone occluded	12		24	
Vena cava plus a coronary artery	22		8	
Coronary sinus alone occluded	4			
Coronary sinus plus a coronary artery	6			
Anoxemia of whole heart	9			
Anoxemia plus a coronary artery	5			

\* Series 1 includes all those experiments done with the chest and pericardium open widely.

† Series 2 shows the number of experiments with electrograms. All these dogs were used in series 3 also.

‡ Series 3 shows the number of experiments done with the method allowing improved conduction from the anterior surface of the heart to the electrodes.

§ Series 4 is composed of the experiments in which chest leads were used.

and striking elevation of the RS-T interval appeared<sup>3a</sup> (fig 1). It was found, moreover, that each time this artery was clamped, the same type of change appeared in the electrocardiogram.<sup>4</sup>

In the dog, therefore, we are confronted with a situation analogous to that existing in man. When one coronary artery is occluded, a characteristic change appears in the RS-T interval of the electrocardiogram. When another coronary artery is obstructed, no such change develops.

Further experimentation elicited the following facts:

1. The appearance time of the elevation of the RS-T interval, following occlusion of the left posterior circumflex artery, is always less

4. In a previous publication,<sup>3a</sup> two figures were shown in which a deep inversion of the T wave appeared after a descending branch of the left posterior circumflex artery had been clamped. Subsequent experiments have shown that this is sometimes an intermediate step during the development or during the disappearance of the typical elevation of the RS-T interval.

than two minutes (fig 2) It is influenced somewhat by the heart rate, the more rapid the rate, the more quickly the changes tend to appear The data now at hand do not support our earlier impressions<sup>3a</sup> that previous damage to the heart definitely shortens this period

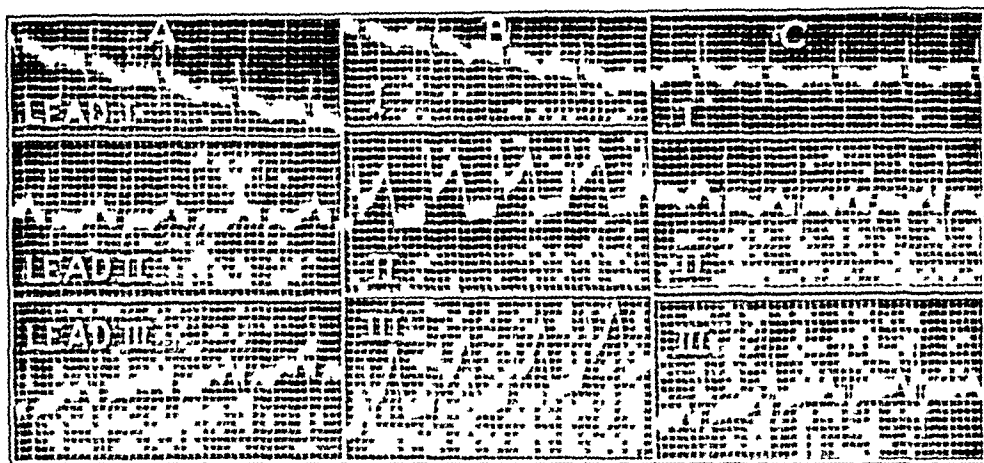


Fig 1—Electrocardiographic changes after occlusion of the posterior circumflex branch of the left coronary artery *A*, control, before the occlusion *B*, one minute after occlusion of the artery The vein was not obstructed A definite elevation of the RS-T interval is seen in leads II and III The clamp was then immediately removed *C*, four minutes after removal of the clamp, showing a disappearance of the electrocardiographic change

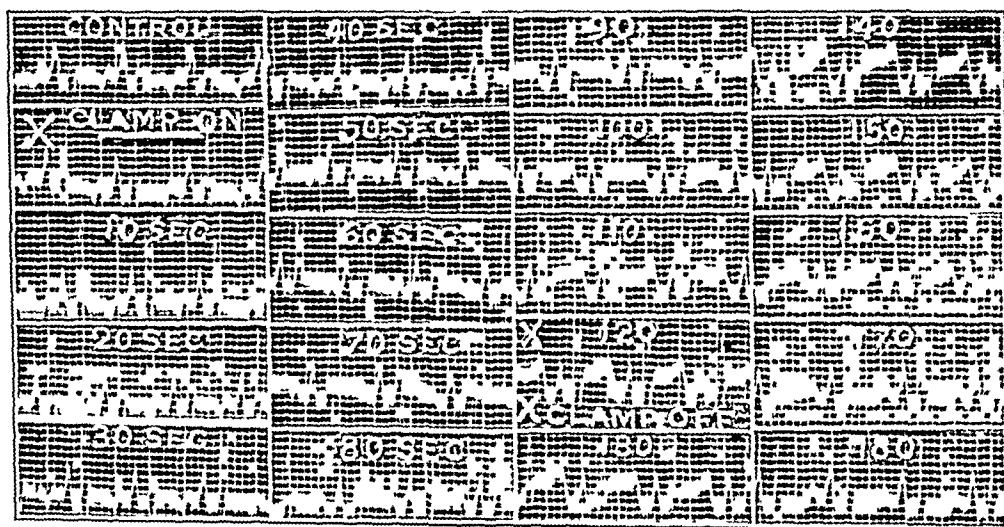


Fig 2—The rate of appearance and disappearance of the elevation of the RS-T interval after occlusion of the posterior circumflex branch of the left coronary artery Tracings were taken in lead II every ten seconds The clamp was removed after one hundred and twenty seconds A definite elevation of the RS-T interval is seen in ninety seconds It disappeared sixty seconds after removal of the clamp, although changes in the T wave are still present

2 The appearance of the elevation of the RS-T interval is not dependent on the simultaneous obstruction of accompanying veins, as

suggested by Feil, Katz, Moore and Scott<sup>3b</sup> Occlusion of the accompanying veins does not even tend to accelerate the development of this change Furthermore, the coronary sinus can be clamped for at least five minutes without producing an RS-T elevation, despite a marked congestion of the coronary veins<sup>5</sup> At the end of this period, if the left posterior circumflex artery is clamped without removing the coronary sinus clamp, the elevation of the RS-T interval does not appear more readily than when the artery alone is occluded

3 The appearance or the nonappearance of the typical deviation of the RS-T interval in the first series of experiments did not seem to be entirely dependent on the size of the infarct<sup>6</sup> When both the right coronary artery and the anterior descending branch of the left coronary artery are occluded simultaneously and the entire anterior surface of the heart is deprived of its arterial blood supply, no definite

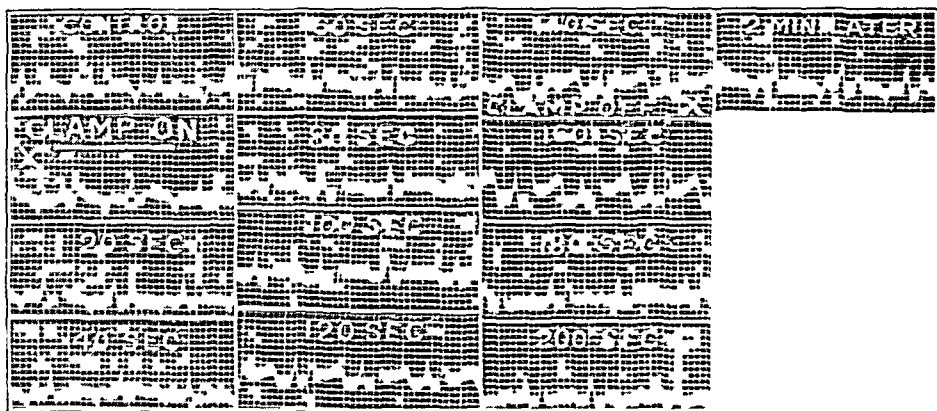


Fig 3—Elevation of the RS-T interval produced by clamping of one of the descending branches of the left posterior circumflex coronary artery. Tracings were taken in lead II every twenty seconds. At one hundred seconds, the change was definitely present. It had practically disappeared sixty seconds after the removal of the clamp.

change appears in the electrocardiogram. However, when one of the descending branches of the left posterior circumflex artery is clamped and a much smaller area of the myocardium is infarcted, elevation of the RS-T interval appears rapidly (fig 3).

5 J. Cohnheim and A. von Schulthess-Rechberg (Ueber die Folgen der Kranzarterien verschliessung für das Herz, Virchows Arch f. path. Anat. **85** 503, 1881) observed that the heart would continue to beat for an indefinite time (over thirty minutes) after ligation of the coronary sinus, without apparent impairment of its power. They also observed that ligation of the accompanying veins with a coronary artery did not accelerate the death of the animal.

6 For want of a more accurate and concise word, the term "infarct" is used in this article to signify a section of the myocardium the arterial blood supply of which has been temporarily interrupted. "Potential infarct" would be more strictly correct.

Therefore, under the conditions of these experiments, the appearance or the nonappearance of a deviation of the RS-T interval from the iso-electric line after occlusion of a coronary artery seems to be dependent in some way on the position which the resulting infarct occupies in the heart. An anterior infarct causes no definite change in the electrocardiogram. On the other hand, a posterior infarct, even though smaller, causes a well defined elevation of the RS-T interval.

Two possible explanations for this phenomenon present themselves (1) an anterior infarct does not cause a change in the action current of the heart, and (2) it produces a change in the action current, but this change is not recorded in the limb leads of the electrocardiogram.

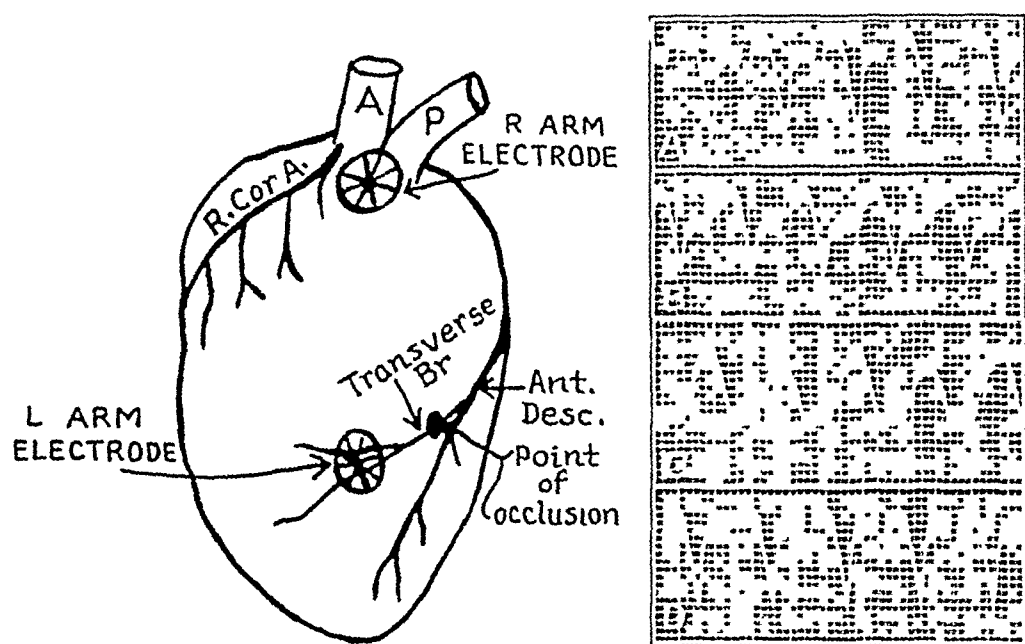


Fig. 4—Occlusion of a small transverse branch of the anterior descending branch of the left coronary artery. Electrodes placed directly on the surface of the heart. The positions of the electrodes and the point of occlusion are indicated in the diagram. Since the left arm electrode was on the infarcted area, an elevation of the RS-T interval of the electrogram occurred. It disappeared completely within four minutes after the clamp was removed. *A*, control; *B*, tracing taken one minute after occlusion of the transverse branch of the left anterior descending coronary artery; *C*, tracing taken one minute after *B*, clamp still in place. The occlusion was then released; *D*, four minutes after removal of the clamp.

In order to test the first hypothesis, electrodes<sup>7</sup> were placed directly on the surface of the heart, and the various anterior arteries were clamped. It was found that a deviation of the RS-T interval will appear in the electrogram within two minutes after occlusion of either the right coronary artery or the anterior descending branch of the

<sup>7</sup> The type of electrodes described by T. Lewis (*The Mechanism and Graphic Registration of the Heart Beat*, London, Shaw & Sons, Ltd., 1925) was used.



left coronary artery if one electrode is located on the infarcted area. Even small infarctions on the anterior surface of the heart cause changes in the RS-T interval if the electrodes are suitably placed (fig 4). The direction of the deviation of the RS-T interval depends on which electrode is situated on the infarct. When the right and the left arm lead wires are used, an infarction under the right arm electrode produces a depression of the RS-T interval (fig 5), an infarction under the left arm electrode produces an elevation of the RS-T interval (fig 4). We do not mean to imply that changes in the RS-T interval fail to appear unless one of the electrodes is located directly on the area of infarction. If, for instance, the right arm electrode is

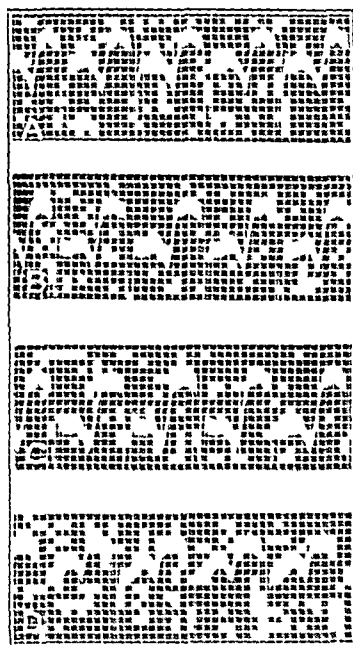
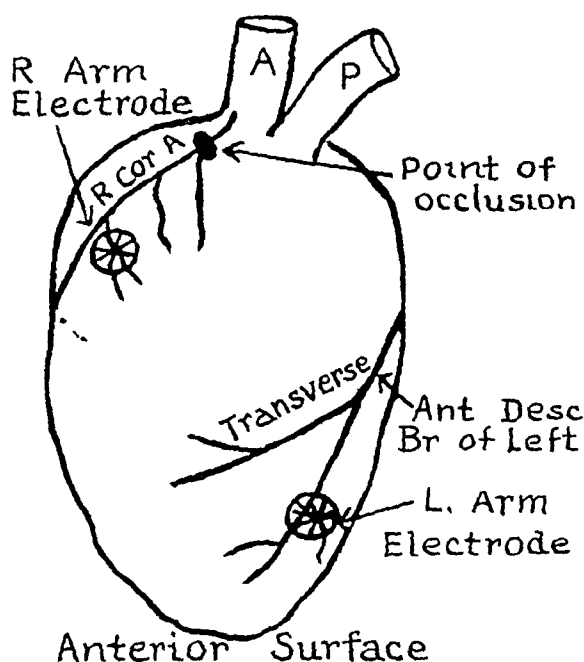


Fig 5—Electrogram resulting from occlusion of the right coronary artery. The positions of the electrodes and the point of occlusion are shown in the diagram. A slight depression of the RS-T interval was present in the control. This may have been due to previous damage to the circulation in this area. Since the right arm electrode was on the infarcted area, a depression of the RS-T interval was recorded. Four minutes after the removal of the clamp, the tracing had practically returned to its previous state. A, control; B, tracing taken one minute after occlusion of the right coronary artery; C, tracing taken one minute after B, clamp still in place. The clamp was then removed; D, four minutes after removal of the clamp.

placed on the lower anterior surface of the heart and the left arm electrode is placed on the left leg, a posterior infarct will produce an elevation of the RS-T interval in this lead; i.e., a deviation in a direction opposite to that produced by an anterior infarct.

It appears, therefore, that whenever infarction of an appreciable section of the surface of a dog's heart occurs, a change rapidly takes

place in the action current of the infarcted area, and within two minutes a deviation of the RS-T interval from the iso-electric line is recordable from this area. Quite evidently, then, the nonappearance

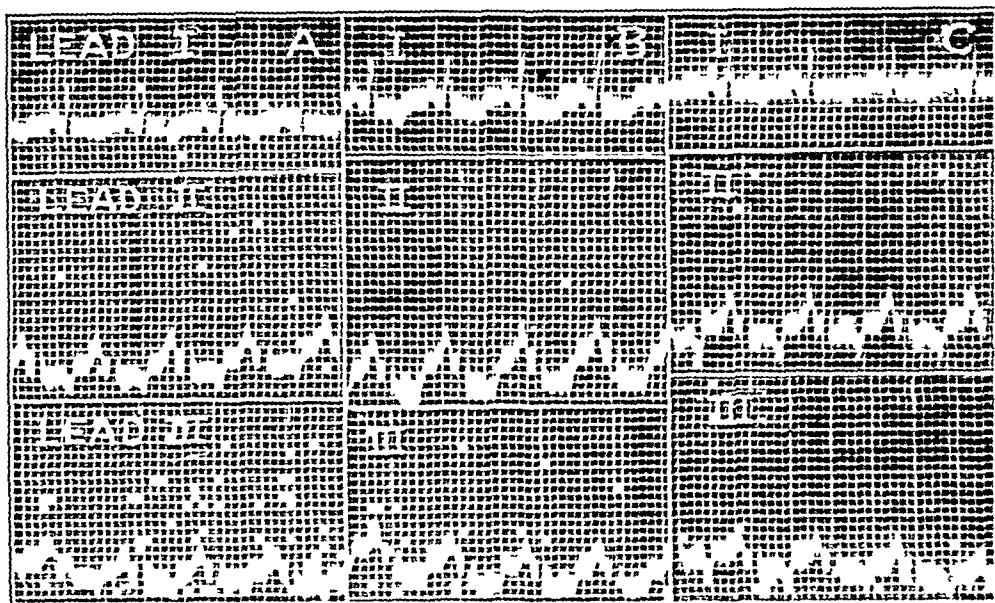


Fig 6—Occlusion of the right coronary artery, conduction from the front of the heart improved *A*, control *B*, three minutes after the occlusion, showing a depression of the RS-T interval in leads II and III and a deeper inversion of  $T_1$ . The clamp was then removed *C*, five minutes after the removal of the clamp



Fig 7—Occlusion of the anterior descending branch of the left coronary artery, conduction from the front of the heart improved *A*, control *B*, one and a half minutes after the artery was occluded  $T_2$  and  $T_3$  have become upright. The clamp was then removed *C*, four minutes after removal of the clamp

of changes in the RS-T interval following anterior infarction in our earlier experiments was due merely to a failure to record an electrical

change which was taking place. It was not due to the fact that a change in the action current had failed to develop.

The next step, therefore, was to determine the cause of our previous failure to record this change in the action current after the anterior arteries had been occluded. On reconsideration of our technic, it occurred to us that the entire anterior surface of the heart had been exposed to the air, the posterior surface had been in intimate contact with the pericardium and the posterior mediastinal structures. It was thought that the failure to record electrocardiographic changes after anterior infarction might be dependent on inadequate electrical conduction from the anterior surface of the heart to the limbs. Conse-



Fig 8—Occlusion of the right coronary artery. Four leads were used. Lead IV was taken from electrodes placed on the anterior and posterior surfaces of the wall of the chest. The anterior one was placed opposite the fourth, fifth and sixth ribs, immediately to the right of the sternum, and was connected to the right arm lead wire. The posterior one was placed opposite the anterior one, just to the left of the spine, and was connected to the left arm lead wire. *A*, control; *B*, tracing taken during the second minute after clamping of the right coronary artery; *C*, tracing taken during the fifth minute after the occlusion, the clamp was still in place. A depression of the T wave in lead I and of the RS-T interval in leads II, III and IV is seen. A slowing of the heart rate is apparent. The clamp was then removed. *D*, four minutes after removal of the clamp.

quently, in the next group of experiments the pericardium was not widely opened. The arteries were approached through small slits in this membrane, and its connections with the anterior wall of the chest and the diaphragm were left intact. With this technic it is possible to record certain changes in the electrocardiogram after occlusion of

the anterior arteries. These changes are specific for each of the two arteries. Occlusion of the right coronary artery regularly produces a depression of the T wave and the RS-T interval (fig 6). Occlusion of the anterior descending branch of the left coronary artery changes the T wave from negative to positive (fig 7). Certain of our tracings also show a slight slurring of the terminal portion of the downstroke of R.

These experiments show that specific changes can be produced in the electrocardiogram of the dog by clamping the right coronary artery and the anterior descending branch of the left coronary artery, as

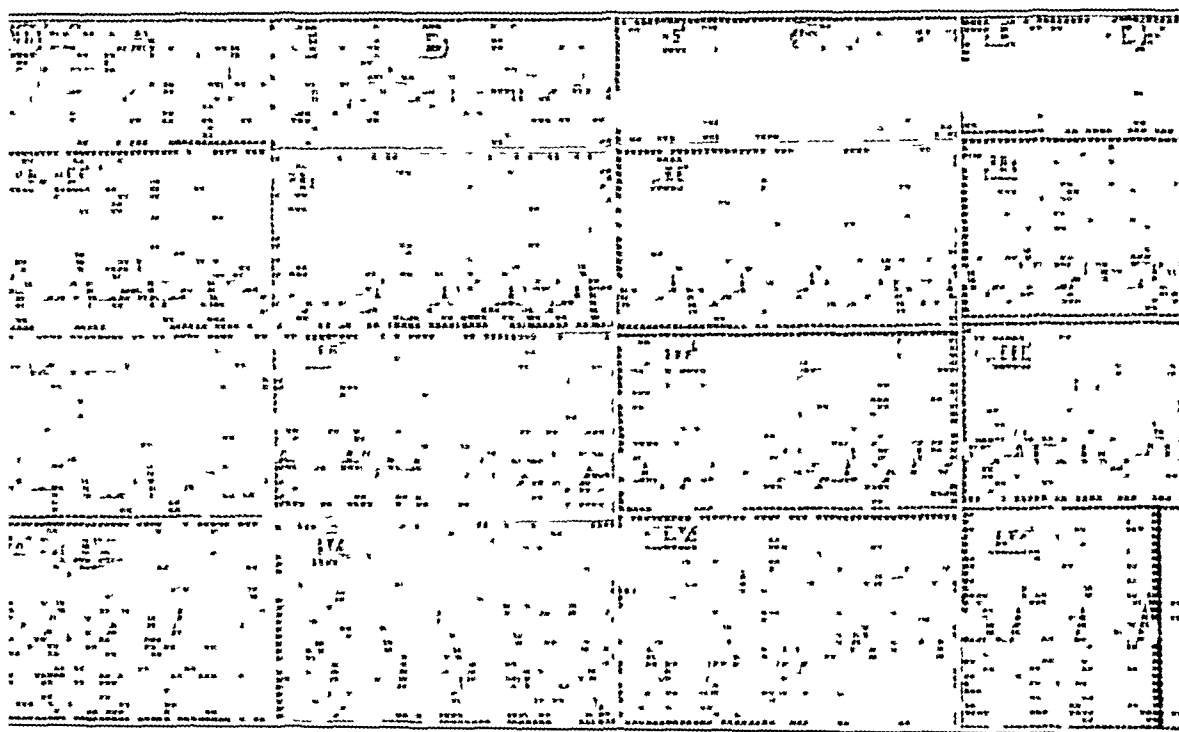


Fig 9—Occlusion of the anterior descending branch of the left coronary artery—four leads. Preparation made as for figure 8. *A*, control. *B*, tracing taken during the second minute after clamping of the artery. The T wave in leads II and III have become upright. The RS-T interval in lead IV is depressed. *C*, tracing taken during the third minute after clamping of the artery.  $T_2$  and  $T_3$  show no further change. The RS-T interval in lead IV is more deeply depressed. The clamp was then removed. *D*, tracing taken five minutes later, showing disappearance of the changes.

well as by clamping the left posterior circumflex. The results fall in line with the observations made in man by Barnes and Whitten.<sup>8</sup> Nevertheless, although these changes in the dog are specific for each artery, no deviation of the RS-T interval followed occlusion of the left anterior descending artery. Moreover, although failure of conduction from the

<sup>8</sup> Barnes, A. R., and Whitten, M. B. Study of the R-T Interval in Myocardial Infarction, *Am Heart J* 5: 142 (Dec) 1929.

anterior surface of the heart was a factor in our experiments, it would not be likely to occur in man. Consequently, it could not account for a failure of development of electrocardiographic changes following acute coronary occlusion in human beings.

These considerations led to another set of experiments in which the position of the electrodes on the surface of the body was changed. In addition to the three conventional leads, another lead was used. The electrodes were placed directly on the anterior and posterior surfaces of the wall of the chest. The right arm lead wire was attached to the anterior electrode, the left arm lead wire was connected to the posterior one. Certain other alterations in technic were made. The animal was turned partly on the right side. The chest was opened



Fig 10—Occlusion of the posterior circumflex branch of the left coronary artery—four leads: *A*, control; *B*, tracings taken between forty-five and ninety seconds after occlusion of the artery. The typical elevation of the RS-T interval is seen, beginning in leads II and III, and well developed in lead IV. The clamp was then removed. *C*, four minutes later, showing disappearance of the changes

on the left.<sup>9</sup> The heart was approached through as small an incision as possible. After isolation of the coronary arteries, the chest was filled with warm physiologic solution of sodium chloride in order to insure adequate conduction from all surfaces of the heart.

Figures 8, 9 and 10 show the results obtained with this technic by clamping the right coronary artery, the anterior descending branch

<sup>9</sup> The right coronary artery was isolated through a preliminary incision on the right side, this incision was closed before we proceeded to the other side. By means of a thread placed under the right artery, this vessel could later be reached and clamped through the incision on the left side.

of the left coronary artery and the posterior circumflex branch of the left coronary artery, respectively. It is apparent that within two minutes after the occlusion of any one of these arteries, a change in the RS-T interval of the electrocardiogram appears in one or more of the four leads. In the case of the right and the left posterior circumflex arteries, this change appears in several leads. When the left anterior descending artery is occluded, a deviation of the RS-T interval appears only in the anteroposterior chest lead.

Thus, finally, the cause becomes apparent why we and other workers<sup>3b</sup> had previously failed to record deviations of the RS-T interval after occlusion of the anterior descending coronary artery. The change

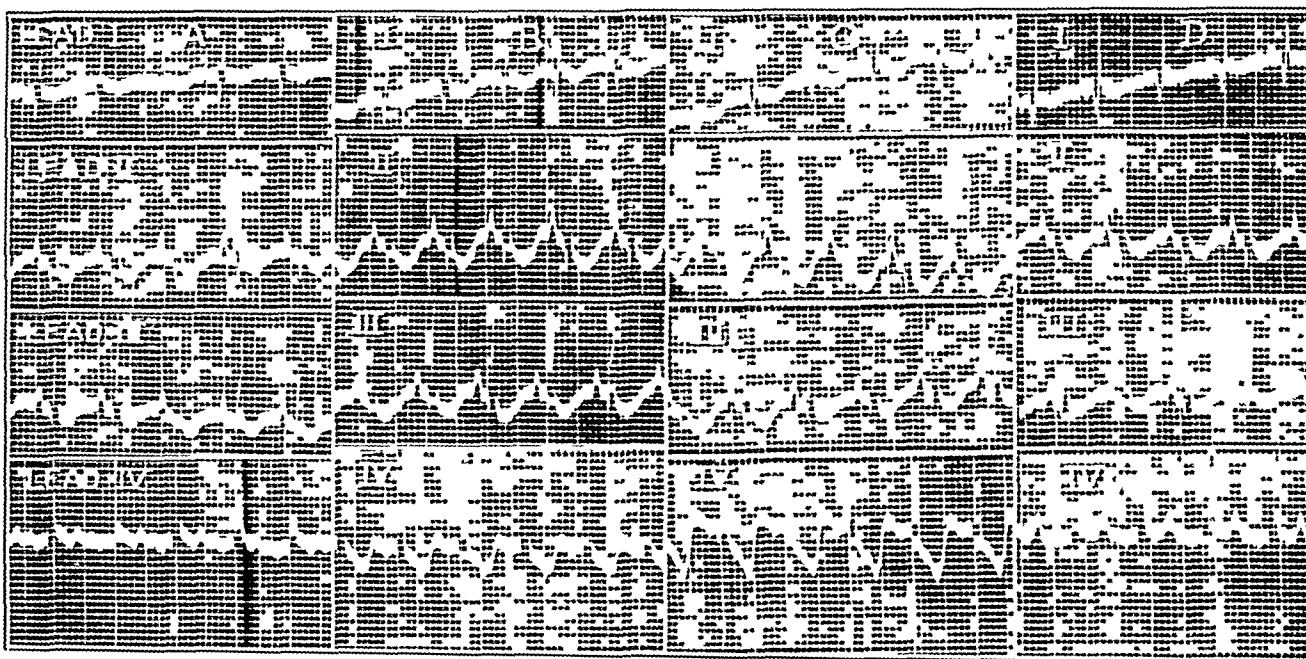


Fig 11—Occlusion of the transverse branch of the left anterior descending coronary artery—four leads. *A*, control. *B*, tracing taken during the second minute after clamping of the artery.  $T_2$  and  $T_3$  do not become upright, as when the main artery is clamped.  $T_4$  and RS- $T_4$  are beginning to invert. *C*, tracing taken during the third minute after occlusion.  $T_2$  and  $T_3$  are the same as in *B*. The RS-T interval in lead IV is distinctly depressed. The clamp was then removed. *D*, five minutes later, the changes have disappeared.

in the action current had occurred each time the artery was clamped. All that was necessary to record it in the electrocardiogram was first, satisfactory conduction from the anterior surface of the heart to the surface of the body, and second, a departure from the three conventional leads and the application of the electrodes to the front and the back of the wall of the chest.

The discovery of the latter fact led us to use an anteroposterior chest lead in the study of human coronary occlusion. In a previous

publication,<sup>9a</sup> a case of acute myocardial infarction was reported in which the chest lead showed a marked deviation of the RS-T interval from the iso-electric line when the conventional three leads showed no such phenomenon

#### COMMENT

It is apparent, therefore, that infarction can occur, both in the dog and in man, in such a position in the heart that it will produce a deviation of the RS-T interval from the iso-electric line in an anteroposterior chest lead, but not in the three conventional leads. On the other hand, in some cases the routine electrocardiogram may show the deviation of the RS-T interval when the anteroposterior chest lead does not.<sup>10</sup>

We have not determined how large an infarct must be in order to produce a deviation of the RS-T interval which is recordable from the surface of the body. We do know, however, that occlusion of a relatively small branch of the left anterior descending coronary artery in the dog will produce such a change in the chest lead (fig 11).

Einthoven and his co-workers,<sup>11</sup> Wilson<sup>12</sup> and Craib,<sup>13</sup> have pointed out the fundamental electrophysical laws which govern the contour of electrocardiograms recorded from various parts of the body. Consequently, a discussion of the factors that determine the appearance or the nonappearance of deviations of the RS-T intervals in various leads need not be undertaken in this article. Suffice it to say that it may be advisable to use three leads in addition to the conventional limb leads in the study of patients with coronary occlusion: (a) an anteroposterior chest lead, (b) a lead from the anterior surface of the chest to the left leg and (c) one from the posterior surface of the chest to the left leg. These six leads, three of which are situated in each of two planes perpendicular to each other, should serve to detect the majority of cardiac infarcts. Whether there are areas in the myocardium

9a Wolferth, C. C., and Wood, F. C. The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads, *Am J M Sc* **183** 30 (Jan) 1932

10 Wolferth, C. C., and Wood, F. C. Further Observations upon the Use of Chest Leads in the Electrocardiographic Study of Coronary Occlusion, *M Clin North America* **16** 161 (July) 1932

11 Einthoven, W., Fahr, G., and deWaart, A. Ueber die Richtung und die manifeste Grosse der Potentialschwankungen im menschen Herzen und uber den Einfluss der Herzschlage auf die Form des Elektrokardiogramms, *Arch f d ges Physiol* **150** 275, 1913

12 Wilson, F. N. The Distribution of the Potential Differences Produced by the Heart Beat Within the Body and at Its Surfaces, *Am Heart J* **5** 599 (June) 1930

13 Craib, W. H. The Electrocardiogram, Medical Research Council, Special Report Series, no 147, London, His Majesty's Stationery Office, 1930

where infarction can occur without producing deviations of the RS-T interval in any of these leads, we do not know

Our experiments on the dog and our observations on man<sup>14</sup> indicate the probability that chest leads may be of considerable help in the localization of myocardial infarcts.<sup>8</sup> When the electrodes are applied to the thoracic wall of a dog, as we have specified, the RS-T interval is depressed by an anterior infarct, whereas it is elevated by a posterior one. These results are similar to those obtained with leads placed directly on the heart (figs 4 and 5). When the right arm electrode is over the infarcted area, the RS-T interval is depressed. When the left arm electrode is over the infarcted area, the RS-T interval is elevated. It is possible, therefore, that a fair degree of accuracy may be attainable in the localization of myocardial infarcts in man by noting which position of the electrodes on the chest gives a maximum deviation of the RS-T interval and by observing the direction of this deviation.

In our early work with direct and semidirect leads (Wilson<sup>12</sup>) it was thought that the change in the action current produced by an infarct affected only the electrode which was placed directly on or over the lesion. However, as we have previously intimated, this is not the case. When the following three leads are used: (a) an antero-posterior chest lead, (b) a lead from the anterior surface of the chest to the left leg and (c) one from the posterior surface of the chest to the left leg, a posterior infarct may cause an elevation of the RS-T interval in (a) and (b) and no deviation of this interval from the iso-electric line in (c).

It must be emphasized here that the dog's heart differs from the human heart in certain important anatomic respects. Therefore, although certain general principles mentioned in this paper apply equally to both, certain specific results of our experiments are not necessarily transferable to man.

The interpretation of human tracings taken by chest leads is dependent on an adequate series of normal controls. Only a small beginning has been made in assembling such a series. When we know exactly what to expect in normal subjects, chest leads may be of considerable use in routine electrocardiography. Localized myocardial lesions of a chronic nature might well be present without producing any abnormalities in the conventional electrocardiogram. In certain cases it may be possible to discover such lesions by means of chest leads.

The question of the appearance time of the changes in the RS-T interval after coronary occlusion merits further discussion. Hurxthal<sup>15</sup>

<sup>14</sup> Wolferth and Wood (footnotes 9a and 10)

<sup>15</sup> Hurxthal, L. M. The Appearance Time of T Wave Changes in the Electrocardiogram Following Acute Coronary Occlusion, *Arch Int Med* **46** 657 (Oct) 1930



has investigated this problem in man. It is well known that a three lead electrocardiogram taken on the day of onset may show no change in the RS-T interval, and that this change may appear subsequently in a tracing taken hours or days later. This has given rise to an impression that the changes of the RS-T interval in coronary occlusion take hours or days to develop. However, when a dog's coronary artery is clamped, the deviation of the RS-T interval dependent on that occlusion appears within two minutes. It is not readily conceivable, therefore, that a similar change in the action current takes much longer to develop in man. Failure in the past to record this change promptly after the onset of an attack of coronary occlusion may have been due to one of two causes: (1) the infarct was too small to produce deviations of the RS-T interval which were recordable at the surface of the body, or (2) the lesion was situated in a part of the heart where infarction does not produce changes in the RS-T interval in the conventional limb leads<sup>16</sup>. Subsequent development of deviations of the RS-T interval may be due to an extension of the thrombosis into other coronary arteries, thereby either enlarging the lesion or extending it into areas which will affect the limb leads. Occasionally, the late appearance of changes in the RS-T interval may be due to the fact that the original attack is caused by an incomplete arterial obstruction, giving rise to pain, but not to changes in the action current. Later, when the occlusion becomes complete, the change in the action current appears. There is no evidence that the change in the action current and the pain appear simultaneously, when a disturbance occurs in the arterial circulation of the heart.

Feil, Katz, Moore and Scott<sup>3b</sup> ligated the left anterior descending coronary artery. No change occurred in the RS-T segment of the electrocardiogram. After a certain number of minutes had elapsed, the inferior vena cava was clamped. An elevation of the RS-T interval appeared, it disappeared when the vena cava was released. Their conclusion was "that RS-T deviation is a manifestation of myocardial ischaemia, in the production of which coronary occlusion is one factor." It appears to have been their impression that coronary occlusion alone will not cause a deviation of the RS-T interval and that, in addition, a reduction of blood pressure is necessary to bring about this change in the electrocardiogram. Our experiments (fig 9) show that the data on which this conclusion is based are inadequate, changes in the RS-T interval are recordable in experiments of the type performed by these workers, provided chest leads are employed and satisfactory conduction

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<sup>16</sup> An instance of this second type has been published<sup>9</sup> in which the antero-posterior part of the chest had alone showed the change.

is obtained from all surfaces of the heart. We have not recorded the blood pressure in our animals. Consequently, our data do not refute their stated conclusion. It is clear, however, that no additional impairment of the coronary circulation or of the general circulation is necessary for the production of deviations of the RS-T interval beyond that produced by occlusion of a coronary artery. The experimental results of Feil and his co-workers might be explained if a reduction of blood pressure could be shown to cause enlargement of an already existing infarct. However, further work is necessary to substantiate this speculation.

Our observations on the results of clamping the inferior vena cava are difficult to interpret. Occlusion of this vessel alone depresses the RS-T interval of the electrocardiogram, reduces the size of the heart and slows its rate markedly. When the vena cava is clamped five minutes before, or simultaneously with, the left posterior circumflex artery, the appearance of the elevation of the RS-T interval seems to be retarded slightly. This may be dependent on the slowed heart rate. Further experimentation is necessary to determine the electrocardiographic results of clamping the vena cava, with and without coronary occlusion.

Gruber and Kountz<sup>17</sup> produced elevations of the RS-T interval in the limb leads of the electrocardiogram of dogs by applications of pitressin to the heart, as well as by the intravenous injection of this drug. The changes that they report are the typical changes in the left posterior circumflex artery. It is probable that this artery took part in the general coronary vasoconstriction which occurred in their experiments, since in our work this vessel was the only one that would produce an elevation of the RS-T interval in the limb leads.

We have not studied the electrocardiographic phenomena of infarction confined to the ventricular septum. The septal branch of the left anterior descending coronary artery, which supplies this part of the heart, lies deeply, and its operative approach is difficult. Kahn,<sup>18</sup> however, developed a technic for occluding this vessel. His tracings, although complicated by ischemia of the branches of the bundle of His, show a definite depression of the RS-T interval of the electrocardiogram in lead II.

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17 Gruber, C. M., and Kountz, W. B. Electrocardiogram of Non-Anesthetized Dogs as Modified by Intravenous Injection of Pitressin, Atropine Sulphate and Vagus Section, *J. Pharmacol. & Exper. Therap.* **40**:253 (Nov.) 1930, The Electrocardiographic Changes in Anoxemia, *Proc. Soc. Exper. Biol. & Med.* **27**, 170 (Dec.) 1929, Effect of Pitressin upon the Heart, *ibid.* **27**, 161 (Dec.) 1929.

18 Kahn, R. H. Elektrokardiogrammstudien, *Arch. f. d. ges. Physiol.* **140**, 627 (June) 1911.

It might be well to record here the relative immediate danger to the dog of clamping the various coronary arteries. Ventricular fibrillation is the usual terminal event in experiments on coronary occlusion. It occurs most rapidly when the left posterior circumflex artery is occluded, within three or four minutes as a rule. It develops more slowly after obstruction of the left anterior descending artery. The least danger of early fibrillation seems to result from right coronary occlusion<sup>19</sup>. Clamping of both the right and the left anterior descending arteries did not seem to be as immediately dangerous to the life of the animal as clamping of the left posterior circumflex alone. We do not understand the reason why occlusion of the latter artery should be particularly prone to cause ventricular fibrillation. The question arises as to whether there is an area in the distribution of this artery which, when deprived of its blood supply, is especially likely to cause fibrillation of the ventricles. The coronary sinus and the inferior vena cava may be clamped for relatively long periods without endangering the life of the animal<sup>5</sup>.

Our previous observations<sup>3a</sup> concerning extrasystoles in experimental coronary occlusion have been confirmed. This type of arrhythmia almost never appears during the first two minutes after obstruction of a coronary artery. It appears later, and is often an indicator of imminent ventricular fibrillation. It is possible that our results have differed from those of other observers either because of the type of anesthesia used, or on account of our care to avoid mechanical stimulation of the myocardium.

Other disturbances of rate and rhythm of the heart were observed. Simple bradycardia, with or without ventricular escape, was noted after occlusion of the right coronary artery and obstruction of the vena cava. Occlusion of the left posterior circumflex artery frequently produced heart block. Auricular fibrillation and paroxysms of auricular and ventricular tachycardia were seen occasionally.

#### SUMMARY

1 The dog presents a situation analogous to that existing in man, with respect to occlusion of the coronary arteries. Infarction in some parts of the heart produces a deviation of the RS-T interval from the iso-electric line in the conventional electrocardiogram. Infarction in other parts of the heart does not.

2 Electrograms show that the failure of certain infarcts to affect the limb lead electrocardiogram is not due to a failure of the develop-

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<sup>19</sup> The experiments of Smith<sup>1</sup> show a high mortality from ligation of the right coronary artery. They are, however, of a nature somewhat different from ours.

ment of changes in the action current in the infarcted area. By means of direct heart leads, deviations of the RS-T interval are recordable within a few minutes after infarction of any part of the surface of the heart.

3 If conduction from all surfaces of the heart is adequate and if an anteroposterior chest lead is used in addition to the routine limb leads, a deviation of the RS-T interval can be recorded in one or more leads after occlusion of any one of the three main coronary arterial trunks. This is likewise true of occlusion of some of the branches of these arteries.

4 Deviation of the RS-T interval due to occlusion of the left anterior descending coronary artery appears in only one of these four leads, the anteroposterior chest lead. Likewise, in man, infarcts in some parts of the heart fail to produce deviations of the RS-T interval except in certain leads which heretofore have not been used as a routine measure.

5 When the right and the left arm lead wires are used and when the electrodes are placed on opposite sides of the chest, an infarct located beneath the former produces a depression of the RS-T interval, one located beneath the latter produces an elevation of this interval. The direction of the deviation of the RS-T interval and the lead in which it makes its maximum appearance serve to indicate the location of the infarct. It is therefore probable that more accurate electrocardiographic localization of myocardial infarcts may be attained in man by the use of chest leads in addition to the three conventional ones.

6 Deviations of the RS-T interval after coronary occlusion in the dog appear within two minutes. It is not likely that they take much longer to appear in man.

7 No additional impairment of the coronary circulation or of the general circulation is necessary for the production of deviation of the RS-T interval beyond that produced by occlusion of a coronary artery.

8 The size of an infarct necessary to cause changes in the RS-T interval, recordable from the body surface, has not been determined accurately. It is certain, however, that relatively small infarcts suffice. The optimum points of application of the electrodes for recording electrocardiographic changes after obstruction of the various coronary arteries deserves further investigation.

9 This series of experiments demonstrates that in the dog deviation of the RS-T interval from the iso-electric line is a characteristic result of acute infarction of any part of the surface of the heart. Failure to record this electrocardiographic change in previous similar experiments

has often been due to failure to apply the electrodes to the surface of the body in the proper locations

The necessity for augmenting the three conventional leads is apparent if a more nearly adequate electrocardiographic picture of cardiac events is to be obtained

These experiments were carried on in the Surgical Research Laboratory of the Medical School of the University of Pennsylvania Dr I S Ravdin placed these facilities at our disposal

# IMMUNE REACTIONS IN DIABETES

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AND

HOBART A REIMANN, M D

MINNEAPOLIS

The unfavorable effect of intercurrent infection on diabetes has long been observed. Joslin<sup>1</sup> drew attention to the presence of infection in nearly every case of coma in the pre-insulin era. At present, a diminution of the effectiveness of insulin during infection is common experience.<sup>2a</sup> Although many studies have been devoted to the effects of infection on diabetes, less attention has been given to the underlying cause of the apparent increased susceptibility of diabetic patients to infection. As the number of deaths from coma have decreased within the past decade, the relative incidence of deaths from various infections has increased. In one series,<sup>1</sup> death from infection during diabetes has increased from 8.5 per cent in the Naunyn era to 26.8 per cent at present. Infection, not including tuberculosis and syphilis, was the cause of death in 126 of Warren's<sup>2b</sup> 300 fatal cases. He remarked that whereas arteriosclerosis threatens the diabetic patient who is doing well, infection is the chief danger of patients who are doing poorly. Among his cases, the susceptibility to infection was in proportion to the severity of the diabetes.

Various experimental studies have been made to determine the cause for the decreased resistance of diabetic persons to infection. One of the most popular theories developed in 1904 from the studies of Lassar,<sup>3</sup> who believed that the increased sugar content of the blood and tissues especially favored the growth of staphylococci. Handmann,<sup>4</sup> on the other hand, showed that blood containing 0.5 or 1 per cent of dextrose did not provide better growth conditions for staphylococci in vitro than normal blood. He also showed that the addition of sugar to the blood within limits found in diabetic patients did not decrease the bactericidal power of the serum. He believed that the diminished resistance of most

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From the Department of Medicine, University Hospital, University of Minnesota

1 Joslin, E. P. *Treatment of Diabetes Mellitus*, ed. 4, Philadelphia, Lea & Febiger, 1928.

2 Warren, S. (a) *Pathology of Diabetes Mellitus*, Philadelphia, Lea & Febiger, 1930, (b) p. 154, (c) p. 102.

3 Lassar, O. *Dermat. Ztschr.* **11**, 189, 1904.

4 Handmann, E. *Deutsches Arch. f. klin. Med.* **102**, 1, 1911.

diabetic persons to infection was a problem of cellular rather than of humoral immunity. Recent studies by Hirsch-Kauffmann and Heimann-Trosien<sup>5</sup> showed that hyperglycemic blood from diabetic children without acidosis did not cause an increase of bacterial growth as compared with blood from normal persons, but blood from 3 comatose patients significantly stimulated bacterial growth. The addition of dextrose and acetone bodies apparently was not alone responsible for increased growth, nor could the growth of bacteria be stimulated by hyperglycemia, lipemia or acidosis produced artificially. Rosenthal and Behrendt<sup>6</sup> showed that the addition of pus to insulin *in vitro* abolished the usual effectiveness of insulin in reducing blood sugar when injected into experimental animals.

Other investigators have approached the problem from a different angle. Observations have been made in regard to variations of complement and opsonic index in experimentally depancreatized animals and in diabetic patients. Sweet,<sup>7</sup> working with dogs, found a marked decrease of hemolytic and bacteriolytic complement in pancreatectomized animals. He noted that transient glycosuria produced by phlorhizin or epinephrine caused no change in complement. Rockwood and Beeler<sup>8</sup> found no significant variation of serum complement in diabetic patients. According to the experiments of Da Costa<sup>9</sup> and of Da Costa and Beardsley,<sup>10</sup> the average opsonic index tested with a variety of bacteria was reduced about 30 per cent below the normal in diabetic patients. Bayer and Form<sup>11</sup> noted that insulin increased phagocytosis *in vitro*. Following pancreatectomy, they<sup>12</sup> observed that a decrease of hemolytic complement was temporarily restored to normal by the injection of insulin and dextrose. In several complicated experiments Nozaki<sup>13</sup> showed that the typhoid bacillus agglutinin titer of vaccinated rabbits is temporarily increased by the injection of insulin.

In experiments of a different nature<sup>14</sup> in other diseases that are characterized by the frequency of intercurrent infection, it was shown that the formation of agglutinins was markedly retarded as compared

5 Hirsch-Kauffmann, H, and Heimann-Trosien A. *Klin Wchnschr* **5** 1922 1926

6 Rosenthal, F, and Behrendt, R. *Ztschr f d ges exper Med* **53** 562, 1926

7 Sweet, J E. *J M Research* **10** 255, 1903

8 Rockwood, R, and Beeler, C. Complement in Serum of Diabetic and Uremic Patients, *J Infect Dis* **34** 625 (June) 1924

9 Da Costa, J C, Jr. *Am J M Sc* **134** 57, 1907

10 Da Costa, J C, Jr, and Beardsley, E J G. *Am J M Sc* **136** 361, 1908

11 Bayer, G, and Form, O. *Deutsche med Wchnschr* **52** 784, 1926

12 Bayer, G, and Form, O. *Deutsche med Wchnschr* **52** 1338, 1926

13 Nozaki, M. *Keijo J Med* **1** 248, 1930

14 Chung, H L, and Reimann, H A. Antibody Formation in Kala-Azar, *Arch Int Med* **46** 782 (Nov) 1930

with their development in normal persons. In other words, clinical evidence of increased susceptibility to intercurrent infection coincided with evidence of diminished antibody response to injected antigens. It was assumed that similar studies might be of value when applied to diabetic patients.

#### METHODS

Twelve diabetic patients and six normal persons for control who had never had typhoid fever, who had never been vaccinated and who were apparently free from other infection were vaccinated with "triple typhoid" vaccine in the usual manner, that is, 0.5, 1 and 1 cc of vaccine containing 1,000 million heat-killed *Bacillus typhosus* and 750 million each of *B. paratyphosus* A and B per cubic centimeter (prepared by the Division of Preventable Diseases, Minnesota Department of Health) was injected subcutaneously at five day intervals. Because of the large amount of technical work involved, it was found convenient to observe groups of

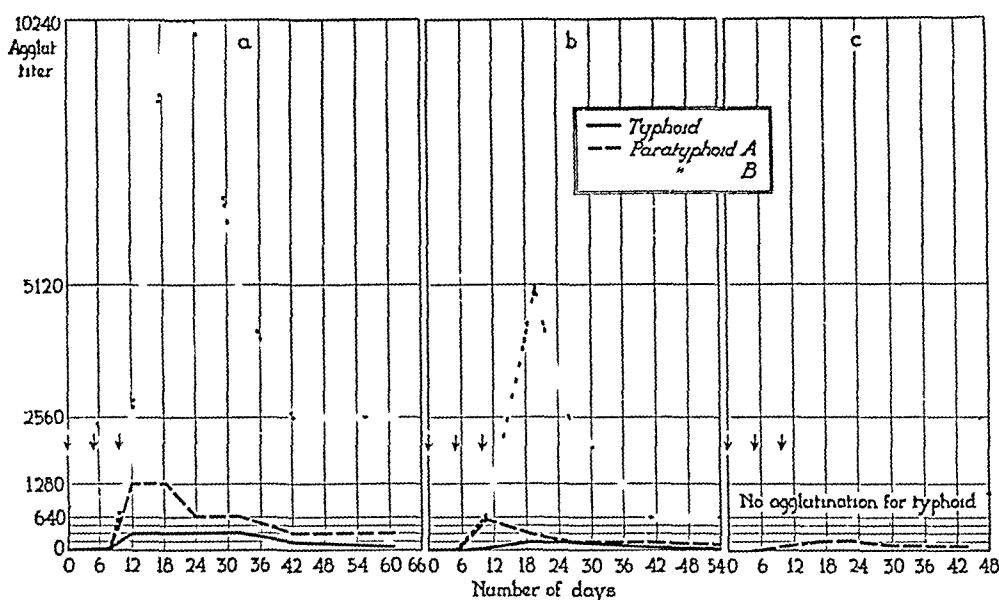


Chart 1—The agglutinin response following vaccination with typhoid-paratyphoid A and B vaccine in a normal subject (*a*), in a controlled case of diabetes (*b*) and in a severe case of diabetes with acidosis (*c*). The arrows indicate the time of vaccination.

four diabetic patients and two control subjects in separate experiments. Blood was obtained from each subject before each injection of vaccine and at intervals of from five to ten days thereafter for a period of six weeks or more. Serum was removed from the clot and stored in a refrigerator until the completion of each set. Agglutination tests were then made in the usual manner, the macroscopic technic being used. In each experimental group the serums were tested for agglutinins for the three strains of bacilli separately, that is, the titer for *B. typhosus* in all samples of serums at hand was first tested. In the second and third tests, *B. paratyphosus* A and B were used, respectively, so that for the sake of uniformity the same suspension of organisms was tested in each sample of serum under similar conditions.

The time required for the acquisition and selection of diabetic patients suitable for this study necessitated the use of different lots of vaccine, so that a somewhat different antigenic response was produced in the different groups of subjects observed.



## RESULTS

No harmful effects from the injection of vaccine were noted in any of the patients. There was nothing especially striking or correlative between the age of the patient, the duration of the diabetes and the severity of the local or constitutional reaction to the vaccine.

*Agglutinin Formation in Normal Persons*—Agglutinins for B typhosus and B paratyphosus A appeared in each vaccinated subject in titers comparable to those in previous experiments<sup>14</sup> and in those reported by many other observers. The titer usually reached the maximum about three weeks after the first vaccination, it then fell off rather rapidly to a lower titer, which in most instances was maintained beyond the termination of the period of observation. In 5 of the controls, the maximum agglutination titer for B typhosus varied from 160 to 1,280, and in one subject reached 20,480. The titer for B paratyphosus A varied from 640 to 10,240, that for B paratyphosus B in 2 groups of experiments, from 2,560 to 10,240. The agglutinin response for the 3 strains of bacilli in a normal subject is illustrated in chart 1a. The third experimental group received vaccine that failed to provoke agglutinins for B paratyphosus B. Whether this was due to the low antigenic properties of the bacilli or to the absence of the antigen in the vaccine was not determined.

*Agglutinin Formation in Diabetic Patients*—The 12 diabetic patients studied may be divided into (a) 7 patients with cases controlled satisfactorily for periods ranging from several weeks to many months, (b) 2 patients in whom diabetes was uncontrolled, with persistent glycosuria, but without acidosis, and (c) 3 patients with severe diabetes who were first observed and vaccinated during diabetic acidosis.

The agglutinin response in the group of patients with controlled diabetes approached that of normal subjects, but in no instance did the agglutinin titer for any of the 3 strains exceed 5,120. An illustration of agglutinin titer curves in a typical controlled case is shown in chart 1b.

Two patients with uncontrolled diabetes showed distinctly subnormal responses to the 3 strains of bacilli. One of these patients persistently failed to adhere to the proper dietary regimen and in consequence had persistent glycosuria. The other patient had severe diabetes, requiring 75 units of insulin daily.

The most marked deviation from the normal occurred in 3 patients with severe diabetes and acidosis. In these cases the first dose of vaccine was given before the administration of insulin, while the patients were still suffering from acidosis. The 3 patients showed low agglutinin response to certain antigens and no response whatever to others. The administration of insulin and regulation of the diet subsequent to the first injection of vaccine apparently had but little effect on agglutinin

formation One of the normal subjects used as a control for this group showed the highest titer observed—20,480 for B typhosus and 10,240 for B paratyphosus A

In one of the patients, the titer for B typhosus never exceeded 80, and that for B paratyphosus A reached 640, but dropped to 160 at the end of the period of observation In the second patient agglutinins failed to develop for either B typhosus or B paratyphosus B, while the maximum titer for B paratyphosus A reached only 160, as shown in chart 1c The third patient was admitted in a state of precoma with Kussmaul breathing, dehydration, drowsiness, nausea, vomiting and acetonuria The acidosis and diabetes were promptly controlled with insulin Unfortunately, the patient left the hospital fourteen days after the first injection of vaccine At this time no agglutinin for B typhosus had appeared, and the titer for B paratyphosus A had reached 320

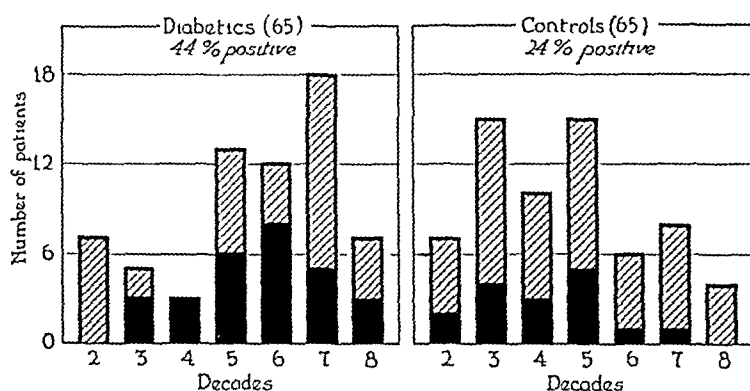


Chart 2—The comparative reactivity of diabetic patients and control patients to the intradermal tuberculin test

*The Tuberculin Reaction in Diabetic Patients*—As a part of the study concerning immune reactions in diabetic patients, the skin reaction to tuberculin was observed in 65 diabetic patients and in 65 nondiabetic control subjects who were apparently free from evidence of tuberculosis. The control subjects were patients in a general hospital group with a variety of other diseases. The Mantoux test was used, 0.1 cc. of a 1:1,000 dilution of old tuberculin was injected intradermally. The skin reactions were read forty-eight hours later. Care was taken to use the same supply of tuberculin for all of the tests. A reaction was considered positive when erythema at least 1 cm. in diameter, with or without induration, appeared after forty-eight hours.

*Results*—Positive reactions appeared in 29 (44 per cent) of the diabetic patients and in 16 (24 per cent) of the control patients. By dividing the subjects tested into age groups by decades, it appears that the diabetic patients who reacted positively are somewhat older than in the control groups (chart 2). The number of observations is obviously

insufficient to draw definite conclusions, but it appears at least that the percentage of diabetic patients who react positively to tuberculin is considerably higher than in the control group of nondiabetic persons

#### COMMENT

The cause for the apparent diminution of agglutinin development in uncontrolled diabetic patients is obscure. Although a number of investigators have suggested that agglutinins originate in the reticulo-endothelial system, in the hematopoietic system or in both,<sup>13</sup> it is impossible to determine definitely the exact site of origin. Experiments on the relationship of changes in the colloidal composition of the plasma to agglutination phenomena are too recent and incomplete to permit discussion in this regard.<sup>15</sup> Evidence exists<sup>2c</sup> that cells of the reticulo-endothelial system in fatal cases of diabetic coma often contain abnormal substances and appear degenerated, but the changes described do not seem to warrant the assumption that these deposits materially effect the production of agglutinins. Nozakı<sup>13</sup> believed that the production of antibody is augmented by various hormones, including insulin. He has shown that when the agglutinin titer for typhoid bacilli in vaccinated rabbits has become constant, an injection of insulin causes a transient increase in the agglutination titer. It is possible, however, that the transient increase as reported by Nozakı may be brought about by the injection of other foreign substances.<sup>15</sup> We have observed the behavior of the agglutinin titer in 2 diabetic patients immediately after a subcutaneous injection of insulin. In one there was a slight increase of titer, while in the other, no change occurred.

From the results in our own series of cases it appears that the agglutinin response to injected antigens is poorest in the uncontrolled cases of diabetes, especially those approaching the state of acidosis and coma. The response is somewhat greater in controlled cases of diabetes and is best in controlled cases of diabetes in which the patients are in apparent good health. In the latter cases the response approaches, and in some cases equals, the development of agglutinins in normal persons.

It was not possible to ascribe the low agglutinin response in certain cases to any definite cause or to demonstrate specific pathologic changes that may be accountable. It is possible that a metabolic perversion or a general lowering of normal functions of the body plays an important rôle in the elaboration of antibodies. Furthermore, there appears to be a coincidence of susceptibility to infection and evidence of decreased agglutinin production in proportion to the severity of diabetes. The stronger response of patients with well controlled diabetes suggests that the deficiency of agglutinin production during the severe states of the

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<sup>15</sup> Reimann, H. A. *Ann Int Med* 6:362 (Sept.) 1932.

disease, as in the case of kala-azar,<sup>14</sup> is transient, and with restoration of the body toward the normal state, immune reactions approach the normal

#### CONCLUSION

The development of agglutinins for typhoid bacilli after the vaccination of diabetic patients and normal persons was observed. In well patients with controlled diabetes, agglutinins developed in titers similar to those in normal persons used as controls. In patient with diabetes that was controlled with more difficulty, the agglutinin response was distinctly weaker. In patients with uncontrolled diabetes with acidosis, the agglutinin response was poor, in a few cases no agglutinin for certain strains appeared. The coincidence of the increased susceptibility of severely ill diabetic patients and the deficiency of demonstrable antibodies suggests a causal relationship of the latter to the former condition.

# EFFECT OF ANOXEMIA ON THE EMPTYING TIME OF THE STOMACH

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The rapid development of travel by airplane has brought to a large number of people a new physiologic environment. A few years ago only the professional balloonist and the mountain climber were subjected to high altitudes, but in recent years the number of people who are subjected to anoxemia has been steadily increasing. From this point of view alone the effect of low oxygen tension on the stomach would be of interest. This combined, however, with the fact that anoxemia is also caused by the various anemias, by diseases of the circulation and of the lungs makes the problem still more interesting. It is well known, for example, that gastric disturbances are not uncommon with cardiac disorders.

It was shown by the authors of this paper in 1930<sup>1</sup> that hunger contractions in the normal dog were greatly decreased in anoxemia. In a subsequent paper<sup>2</sup> it was shown that under similar conditions digestive peristalses, too, were markedly diminished, and that the muscle tone of the stomach was appreciably lowered. As far as we are aware, this work is all that is found in the literature on the motility of the intact gastro-intestinal tract under anoxemic conditions. As hunger contractions and digestive peristalses were both lessened when anoxemia was induced, it was thought well worth while to ascertain the effect of lowered oxygen tension on the emptying time of the stomach.

## METHOD

Six normal dogs averaging about 6 Kg in weight were given a meal consisting of 40 Gm of hamburger steak, 10 Gm of dried ground bread and 50 cc of milk, 15 Gm of barium sulphate was added. The dogs ate this meal with relish. They were then put into a large steel respiratory chamber which could be tightly closed. It was well ventilated, however, by means of an air pump which was kept con-

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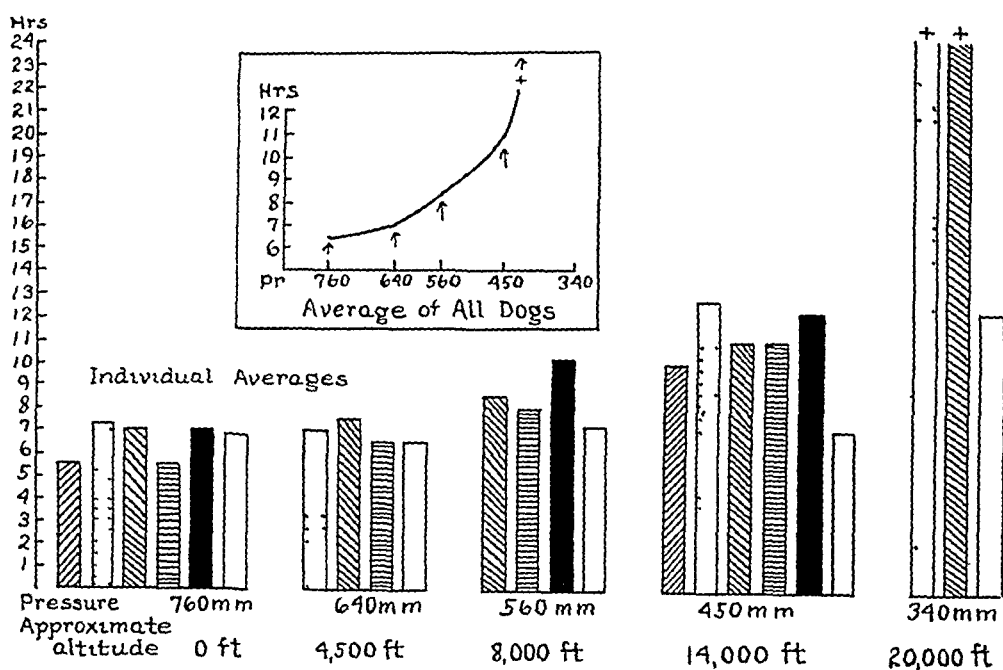
From the Department of Physiology, University of West Virginia, Morgantown.

1 Van Liere, E J, and Crisler, G. The Effect of Anoxemia on Hunger Contractions, *Am J Physiol* **93** 267 (May) 1930.

2 Crisler, G, and Van Liere, E J. The Effect of Anoxemia on the Digestive Movements of the Stomach, *Am J Physiol* **102** 629 (Dec) 1932.

stantly running. The air was drawn out, but a valve opposite the opening through which the pump withdrew the air was left open so that a stream of fresh air was continually flowing through the tank. During the control periods the inside of the chamber was, of course, kept at atmospheric pressure. By means of the fluoroscope the normal emptying time of the stomach was determined for each dog, this was done for a number of days. It was obviously necessary to remove the animals from the chamber in order to examine them under the fluoroscope. This procedure took from five to fifteen minutes, so that an experimental error of thirty minutes was allowed, that is, plus or minus fifteen minutes.

After the control periods were well established, the animals were subjected to a lowered oxygen tension. This was done by partially closing the valve which opened to the outside air so that the pump could withdraw the air somewhat faster than it could enter. The valve was adjusted to whatever pressure was desired.



Effect of anoxemia on the individual emptying time of the stomach in six animals at various pressures. Each animal is represented by the same type of shading under each pressure at which emptying occurs.

In order to obtain the pressure within the chamber, a long glass U-tube filled with mercury up to a level of 380 mm was attached to a meter stick. This mercury manometer was connected with the chamber, the pressure fell as the air was exhausted, and it could be read directly in millimeters of mercury. The large capacity of the air pump provided good ventilation and prevented the accumulation of carbon dioxide, in spite of the fact that the inlet valve was partly closed.

## RESULTS

The accompanying illustration shows the results obtained. The normal emptying time of the stomach varied, but was characteristic for each dog. In the case of two dogs the time was five and one half hours, while in the other four dogs it was longer—from six and three fourths to seven and one half hours. At an air pressure of 640 mm of

mercury there was no predictable lengthening of the emptying time of the stomach, in fact two of the four dogs which were subjected to this pressure showed a slight decrease in the emptying time. At a pressure of 450 mm of mercury, five of six dogs showed a considerable lengthening of the emptying time, requiring as much as five additional hours. Finally, at a pressure of 340 mm of mercury, two of the three animals which were run at this pressure on fluoroscopic examination still showed food in their stomachs at the end of twenty-four hours, and the animal which had been resistant up to this time now also showed a distinct increase in the emptying time. These results are summarized in the table.

*Effect of Anoxemia on the Emptying Time of the Stomach*

Dog	Pressure in Mm of Mercury				
	760	640	560	450	340
	In Hours				
1	5 50			10 00	
2	7 50	7 00		12 75	24+
3	7 00	7 50	8 50	11 00	24+
4	5 50	6 50	8 00	11 00	
5	7 00		10 25	12 25	
6	6 75	6 50	7 25	7 00	12 50
	Per Cent of Normal				
1	100			182	
2	100	93		170	320+
3	100	106	121	157	343+
4	100	118	145	200	
5	100		146	175	
6	100	96	107	104	185

#### COMMENTS

It might appear that the normal emptying time of the stomach in these dogs was rather long, as other writers have reported shorter periods. These workers, however, used a different type of meal. We felt that a meal consisting of hamburger steak and bread and milk was a fairly well balanced diet, and, moreover, the milk gave the meal a desirable consistency. In order to check our control periods, animals were kept in the chamber so that they would be in the same environment, the pressure in the chamber was, of course, atmospheric, and, as mentioned, adequate ventilation was provided.

It is interesting to note that two of four animals showed a slight decrease in the emptying time of the stomach at a pressure of 640 mm of mercury. It would seem that a slight stimulation occurred, further work is needed on this particular point. At a pressure of 560 mm of mercury three of four animals showed a delay in the emptying time of the stomach. This pressure corresponds approximately to 15.35 per cent of oxygen and to an altitude of 8,000 feet. This may be taken as the threshold, there are many regions in southwestern United States that approach this altitude. It would be of interest to know whether any clinical observations have been made on this point.

At a pressure which corresponds to about 14,000 feet and to an oxygen percentage of 12.50, all the animals but one were markedly affected. This is about the altitude of Pike's Peak in Colorado. It is a well known fact that many tourists are afflicted with mountain sickness and often vomit when they arrive at the summit of Pike's Peak. No retching or vomiting movements were noticed in the dogs, but of course they were not subjected to exercise, and it is quite possible that in the case of human beings psychic factors may enter.

At an altitude of 20,000 feet, two animals still showed considerable food in their stomach at the end of twenty-four hours. This is of particular interest, as human beings can get along well at an altitude of 18,000 feet, for example, the natives of Peru, who live in the high Andes, acclimation would enter here without doubt, but to prove this point further work is required.

Owing to the lack of a proper chamber, the work could not be carried out in man, but we feel that man would react in the same way. We hope at some later time to be able to check the results on man.

The cause of the retention of food in the stomach when an animal is subjected to anoxemia is not entirely clear. There are a number of things to consider, such as the circulation of the blood, the reaction of the blood, the question of so-called vagospasm, the question of physiologic oxidations and the like. At the present time, work is in progress to determine the exact mechanism.

#### SUMMARY AND CONCLUSIONS

It was found that under carefully controlled conditions, dogs showed a definite prolongation of the emptying time of the stomach under anoxemic conditions. At a pressure of 560 mm of mercury, which corresponds to an oxygen percentage of 15.35 and to an altitude of 8,000 feet, three of four dogs showed a definite retention of food in the stomach, one dog was resistant. This animal, however, responded to higher degrees of anoxemia. This, then, may be considered the threshold for the average dog. The higher the degree of anoxemia, the greater the prolongation of the emptying time of the stomach. Finally, at a pressure of 340 mm of mercury, which corresponds to an oxygen percentage of about 9.4 and to an altitude of 20,000 feet, two of three dogs which were subjected to this pressure still had food in their stomachs at the end of twenty-four hours. Higher degrees of anoxemia were not used.

Because of the importance of air travel, and because many diseases with which man is afflicted cause anoxemia, it is felt that the results of these experiments are of interest in clinical medicine. The exact mechanism as yet has not been worked out, at the present time further work is in progress.



# CONSUMPTION OF BLOOD SUGAR BY MUSCLE IN THE NONDIABETIC AND IN THE DIABETIC STATE

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It has been established for a number of years (Macleod and Pearce<sup>1</sup>) that the decline in blood sugar which follows complete removal of the abdominal viscera (including the liver) is the same in previously depancreatized as in normal dogs. This observation tended to support the hypothesis that the essential nature of pancreatic diabetes is not an inability of the tissues to consume dextrose. This experiment was criticized on the grounds of its unphysiologic nature and the necessity of keeping the animals under the influence of a general anesthetic. However, it was shown by Mann and Magath<sup>2</sup> in their classic studies on liverless dogs that the decline of blood sugar following hepatectomy is speedier in diabetic dogs than in normal ones. Moreover, Mann and Magath reported an experiment in which complete pancreatectomy was accomplished in a dog which by previous operations had been subjected to a marked reduction in the size of its functioning liver tissue. This animal lived for ten days on a diet of milk, during which time it had neither hyperglycemia nor glycosuria. The general condition of the animal (suppuration of the abdominal wound and the characteristic scum in the conjunctiva) indicated that it was diabetic, as did also its death at the end of ten days, which was inexplicable except on the basis of diabetes. Mann and Magath cautiously refrained from interpreting these experiments as indicating that diabetic tissues possessed an apparently normal capacity to use dextrose, although such experiments taken at their face value could not be interpreted in

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1 Macleod, J J R, and Pearce, R G. *Am J Physiol* **32** 184, 1913

2 Mann, F C, and Magath, T B. Studies on the Physiology of the Liver II The Effect of the Removal of the Liver on the Blood Sugar Level, *Arch Int Med* **30** 73 (July) 1922, III The Effect of Administration of Glucose in the Condition Following Total Extirpation of the Liver, *ibid* **30** 171 (Aug) 1922 IV The Effect of Total Removal of the Liver After Pancreatectomy on the Blood Sugar Level, *ibid* **31** 797 (June) 1923

any other way. Investigators have been loath to accept such a conclusion, since strong evidence exists, on the basis of entirely different experiments, which would lead to the opposite conclusion, viz., that the essential nature of diabetes is an inability of the tissues to derive energy from the disruption of the dextrose molecule. This evidence has been summarized by Lépine according to Geelmuyden<sup>3</sup> as follows:

(1) The administration of dextrose to depancreatized dogs is followed by its prompt quantitative elimination in the urine, (2) administration of carbohydrate to a diabetic dog does not evoke a rise in the respiratory quotient, and (3) the glycosuria of depancreatized dogs is in no way diminished by muscular exercise. We may add that the last fact is true in human beings who have severe diabetes, a condition which approximates complete pancreatectomy, although in the milder form of diabetes muscular exercise may produce an apparently greater tolerance for carbohydrate, owing to an increase in the dextrose equivalent of insulin, which F. N. Allan<sup>4</sup> has shown to be possible.<sup>5</sup>

According to the Hill-Meyerhof theory concerning the rôle of glycogen and lactic acid in muscular contraction, it is difficult to appreciate how the diabetic state could be due to inability of muscle to consume carbohydrate, since depancreatized dogs manifest a certain amount of muscular activity. However, recent work in the field of muscular contraction makes such reasoning unnecessary.

It may be taken for granted that the aforementioned experiments are entirely correct, since they have been repeated by many competent workers. Knowlton and Starling<sup>6</sup> investigated the consumption of dextrose by the normal and the diabetic heart, making use of the just previously developed heart-lung preparation. Their experiments were beautifully executed. They found that the heart muscle of the normal dog consumes about 4 mg. of dextrose per gram of heart muscle per hour. They stated that the power of consuming dextrose was reduced to a minimum or disappeared completely in heart-lung preparations made from animals which had been completely depancreatized several days prior to the experiment. These elegant and classic experiments were substantiated by Maclean and Smedley,<sup>7</sup> who perfused hearts of cats and dogs with Locke's solution and reported that when these were excised from previously depancreatized animals, little or no combustion of dextrose occurred. In spite of these findings by such reputable

3 Geelmuyden, H. C. *Ergebn. d. Physiol.* **22**, 92, 1923.

4 Allan, F. N. *Am. J. Physiol.* **67**, 275, 1924.

5 In some unpublished experiments we have been able to show that severe strychnine spasms in depancreatized dogs augment if anything the glycosuria.

6 Knowlton, E. P., and Starling, E. H. *J. Physiol.* **45**, 146, 1912.

7 Maclean, H., and Smedley, I. *J. Physiol.* **45**, 470, 1913.

workers, their thesis slowly lost ground on the basis that the sugar estimations were unreliable and that the results were explicable on the basis of a higher glycogen content possessed by diabetic heart muscle. Quite recently Cruickshank<sup>8</sup> has repeated the original experiments of Knowlton and Stirling under more carefully controlled conditions, completely vindicating their findings.

One is thus confronted by two sets of apparently contradictory facts. First, the liverless dog possesses the ability of using large quantities of dextrose, so that under certain artificial conditions the diabetic state may be accompanied by neither hyperglycemia nor glycosuria, second, the contracting muscle of the diabetic organism, either intact or in the form of the isolated perfused heart, has largely lost its power to obtain the energy from dextrose. Any one who has worked in this field soon becomes convinced of the essential correctness of these observations. There must be some unifying fact relieving the apparent discrepancy. This we have attempted to find in the following series of experiments.

That there is a fundamental difference in the storage capacity of the diabetic organism for dextrose is not disputed, it is indicated by the following well established observations. (1) The liver of depancreatized animals is practically devoid of glycogen (Minkowski<sup>9</sup>), cardiac muscle has an increased quantity of glycogen in the diabetic state (Cruickshank<sup>10</sup>), (2) whereas the administration of dextrose to a liverless dog is followed by a huge increase in the respiratory quotient (Markowitz,<sup>11</sup> Mann and Boothby<sup>12</sup>), the similar administration of dextrose to a depancreatized and subsequently dehepatized dog is without effect on the respiratory quotient (Markowitz<sup>11</sup>), although in such animals hypoglycemic symptoms develop to which dextrose is an antidote. Soskin<sup>13</sup> recently reported experiments in which completely depancreatized dogs were carefully nursed and fed, with the result that in a number of them the glycosuria largely disappeared. Such animals, it is certain, were completely depancreatized.

From this brief review it is apparent that we are by no means clear as to why under certain conditions diabetic tissues appear to use dextrose and under others appear to have lost this power. We wish to present the thesis, which has inevitably unfolded itself during our experiments, that resting diabetic muscle possesses a power to consume dextrose which is practically, if not completely, indistinguishable from

8 Cruickshank, E. W. H. *Am J Physiol* **90** 322, 1929.

9 Minkowski, O. *Arch f exper Path u Pharmacol* **21** 1, 1886.

10 Cruickshank, E. W. H. *J Physiol* **47** 1, 1913.

11 Markowitz, J. *Am J Physiol* **83** 698, 1928.

12 Mann, F. C., and Boothby, W. M. *Am J Physiol* **87** 486, 1928.

13 Soskin, S. *J Nutrition* **3** 99, 1930.

that of normal muscle. When muscular contraction occurs, however, the extra metabolism imposed on the muscle does not occur by the utilization of blood sugar. It would appear that before dextrose is available to supply energy for muscular contraction it must undergo some sort of elaboration, brought about by insulin. This thesis harmonizes two apparently conflicting sets of experiments. It does not confute the great probability that in the diabetic state dextrose cannot be stored as glycogen in the absence of insulin, a fact that has been well established by Best, Dale, Hoet and Marks<sup>14</sup>

#### I COMPARISON OF THE CONSUMPTION OF DEXTROSE BY THE NON-DIABETIC AND THE DIABETIC HEART-LUNG PREPARATION

We have repeated the experiments of Knowlton and Starling, and find on comparing our data with theirs that the results are identical. The following protocols are typical examples.

1 *Consumption of Dextrose by the Heart-Lung Preparation (Working Muscle)*  
—On June 17, 1931, a heart-lung preparation was made from a dog weighing 10.2 Kg. The heart-lung apparatus contained 150 cc. of heparin in Ringer's solution, most of which was introduced into the animal via the superior vena cava to render its blood incoagulable prior to opening the artificial circuit. It was carefully calculated that 500 cc. of slightly diluted blood was obtained from the animal at the moment of complete isolation of the circuit. The blood in the pulmonary circulation and in the chambers of the heart was included in this estimate. The volume output was adjusted to 1,000 cc. per minute. This quantity was obtained by tying the aorta distal to the cannulated brachiocephalic artery and elevating the posterior extremity of the dog until practically no more blood flowed into the venous reservoir. The inferior vena cava was then tied. A mark was made to indicate the level of blood in the venous reservoir for future calibration, and blood was admitted to the superior vena cava from the reservoir, thus establishing the artificial circuit. The root of one lung was occluded by gastro-enterostomy (Doyen) forceps to minimize loss of blood in the form of pulmonary edema. The temperature of the blood in the venous reservoir was kept constant at  $37 \pm 0.5^\circ\text{C}$ . The peripheral resistance aggregated 90 mm. of mercury, as measured by a mercury manometer connected to the cannula in the brachiocephalic artery. At 11.50 a.m., immediately after isolating the circuit, the blood sugar<sup>15</sup> was 0.272 per cent. This hyperglycemia is constant in all such experiments owing to asphyxial glycogenolysis in the liver. A sample of blood was collected in a test

14 Best, C. H., Dale, H. H., Hoet, J. P., and Marks, H. P. Proc. Roy. Soc., London, s. B, **100** 32, 1926.

15 The Shaffer-Hartmann method (Shaffer, P. A., and Hartmann, A. F. J. Biol. Chem. **45** 365, 1921) for the estimation of blood sugar was used in all experiments. Blood proteins were precipitated according to the Folin-Wu method, and the copper reduction values were transformed to dextrose by means of the table of W. F. Duggan and E. L. Scott (J. Biol. Chem. **45** 365, 1926), a necessary condition for the accurate use of the Shaffer-Hartmann method, since the tables of Shaffer and Hartmann are somewhat inaccurate when tested with pure solutions of dextrose.

tube which was stoppered and incubated in the blood of the venous reservoir as the control sample for glycolysis. At 12 20 p m the blood sugar was 0.240 per cent, at 12 50 p m, 0.190 per cent, at 1 30 p m, 0.158 per cent, and at 1 50 p m, 0.110 per cent. The experiment was now terminated and the sample of blood incubated for glycolysis was then estimated for sugar content, which was 0.248 per cent. The disappearance of sugar by glycolysis was, therefore, 0.024 per cent. This figure was added to the final blood sugar estimate obtained, which made it 0.134 per cent. Therefore, 0.138 per cent blood sugar had disappeared (first blood sugar value minus 0.134) owing to contraction of the heart muscle (neglecting the metabolism of the lungs). At the end of the experiment the heart was in good condition. There was very little pulmonary edema and the experiment could have continued at least another hour. The heart was severed from the great vessels, trimmed of parietal pericardium, opened and mopped free of blood with filter paper. It weighed 88 Gm. The consumption of dextrose was therefore 3.91 mg per gram per hour. This figure is practically identical with that obtained in other experiments performed by us and in those of Knowlton and Starling.

*2 Consumption of Dextrose by the Diabetic Heart-Lung Preparation*—A medium-sized dog, which had been completely depancreatized four days before, was used (March 6, 1931) for a heart-lung perfusion. At 10 30 a m the perfusion was begun under conditions identical to those of the former experiment. The animal's own blood was used and allowed to drip into the venous reservoir up to a previously established mark, which indicated a volume in the circuit of 500 cc. When this level was attained the inferior vena cava was tied and blood was administered to the superior vena cava from the reservoir, thus completing the circuit. At 10 30 a m a sample of blood was taken for a dextrose estimation. The blood sugar value was 0.275 per cent. At the time that this sample was taken, some blood was collected as a control sample for glycolysis. At 11 00 a m the blood sugar value was 0.267 per cent. At 11 30 a m it was 0.233 per cent. The control sample for glycolysis at this time had a sugar content of 0.250 per cent. In the course of an hour therefore, the blood sugar had fallen from 0.275 to 0.233 per cent, or 0.042 per cent, of which 0.025 per cent was due to glycolysis. The consumption of dextrose, therefore, was 0.017 per cent. The experiment was terminated at this point, with the preparation in good condition, and the heart was treated and weighed as in the previous experiment. The weight was 92.5 Gm. The dextrose which was consumed was estimated on the basis of a total volume of 500 cc of blood. This equals 85 mg of dextrose, or a consumption of 0.92 mg per gram of heart muscle per hour, which is approximately one-fourth the normal amount. The glycogen content of the heart was determined at the end of the experiment. This was 0.720 per cent.

The experiments so adequately confirm those of Knowlton and Starling that it may be taken as established that, whereas normal heart muscle consumes 4 mg dextrose per gram per working hour under the conditions described in a heart-lung circuit, the heart muscle of a previously depancreatized dog under identical conditions consumes under one-fourth this quantity. It may be argued that the meager consumption of blood sugar by the diabetic heart is an accident, depending on the greater quantity of glycogen contained by the heart in diabetes. This explanation, plausible though it is, must be rejected for

the following reasons, based on the observations of Knowlton and Stirling<sup>6</sup> and Cruickshank<sup>8</sup>. When the diabetic heart is perfused with normal blood (i.e., removed from a nondiabetic donor) its sugar consumption is normal. The same occurs when insulin is added to the blood of the diabetic heart-lung preparation. It will be shown later that the rate of consumption of blood sugar by diabetic heart muscle corresponds to the rate of consumption of blood sugar by the resting muscle of a liverless dog. A liverless dog requires 250 mg per kilogram per hour for the blood sugar to stay normal. Assuming that the seat of oxidation of blood sugar (Mann and Magath) in a liverless animal is chiefly muscle, which is approximately one third of the body weight, it can be calculated that the consumption of blood sugar by resting skeletal muscle is 250 divided by 3, which equals 0.83 mg per gram per hour. This calculation is, of course, only approximate, since it does not take into account the dextrose consumption of the brain and of other tissues, which, however, are not nearly as bulky. Nevertheless, the general deduction seems inescapable that contracting diabetic muscle (heart) consumes about as much sugar as does resting nondiabetic skeletal muscle per unit weight. Blood sugar apparently is not available in the diabetic state for the purpose of yielding energy for muscular contraction of the heart. Probably one function of insulin is to elaborate the dextrose molecule so that it can serve this purpose.

To obtain further information regarding the plausibility of this hypothesis we undertook to estimate the dextrose requirements of liverless dogs both in the nondiabetic and in the diabetic state and during the conditions of rest and vigorous muscular activity. For this purpose we made use of the recently developed method of one-stage hepatectomy described in a forthcoming paper (Markowitz, Yater and Burrows<sup>16</sup>), by which it is possible to remove the liver of a dog in one stage with reasonable expectations that a vigorous long-lived preparation will result. Accordingly we excised the liver of several dogs after a preliminary fast of twenty-four hours. The subsequent behavior of these animals was identical with those of Mann<sup>17</sup> prepared by the three-stage method. The decline of blood sugar following hepatectomy was studied in a series of such animals. In another series the animals were strychninized sufficiently to induce severe convulsions for an hour or more. To accomplish this it was necessary to inject 0.20 mg of strychnine sulphate per kilogram of body weight intravenously and one quarter of this dose subcutaneously at intervals of fifteen minutes or so, to maintain the animal in the convulsive state.

16 Markowitz, J., Yater, W. M., and Burrows, W. H. A Simple One-Stage Technique for Hepatectomy in the Dog, *J. Lab. & Clin. Med.*, to be published.

17 Mann, F. C. *Am. J. M. Sc.* **161**: 37, 1921.

A number of animals were lost. No matter how severe the convulsions were, the decline of blood sugar was not accelerated. This conclusion was such a difficult one to accept that we repeated the experiments, comparing the decline in blood sugar of etherized liverless dogs with that of liverless dogs which were also kept under ether anesthesia but in which the spinal cord was stimulated thirty times each minute by faradic shocks with the resultant convulsions of the muscles, mainly of the hind limbs. This was achieved by a Lewis rotary interrupter, the stimulating electrode being inserted into the cord at the level of the sixth thoracic segment. Under these conditions also the decline in blood sugar was generally uninfluenced by the muscular contractions. Apparently the decline in the blood sugar of a liverless dog is not a satisfactory criterion of the sugar requirements of working muscle. It may well be that the carbohydrate requirements of muscle are partitioned between the glycogen of the muscle on the one hand and the blood sugar on the other, the latter being spared in hypoglycemia. The plan of experimentation was accordingly changed to the following. The liver was removed from a series of dogs and dextrose was injected intravenously either continuously or every fifteen minutes with the object of establishing the quantity necessary to maintain the blood sugar constant during the first ten hours following removal of the liver. As illustrated by the following protocol this figure is 0.25 Gm. of dextrose per kilogram per hour.

## II EFFECT ON BLOOD SUGAR OF A LIVERLESS DOG OF CONTINUOUS INTRAVENOUS INJECTION OF 0.25 GM. OF DEXTROSE PER KILOGRAM PER HOUR

A female collie, weighing 8.7 Kg., was etherized at 10.00 a. m. on Jan. 6, 1932. At 10.10 a. m. blood was removed for a dextrose estimation. This was 0.183 per cent. At 10.15 a. m. the first incision was made. At 10.40 a. m. the Eck fistula was completed, the stoma being 1.5 cm. long. At 10.48 a. m. the liver was extirpated. During the operation only 15 cc. of blood was lost, an irreducible minimum for this type of surgery. The etherization was discontinued. At 11.00 a. m. the last suture was tied. At 11.04 a. m. the blood sugar was 0.115 per cent (chart 1). By 11.20 a. m. the dog was fully conscious, and continuous intravenous injection of dextrose solution by means of a cannula in a saphenous vein was begun. The dextrose was made up in 12.5 per cent solution in physiologic solution of sodium chloride. It was injected at a constant rate by a continuous infusion apparatus, 17.4 cc. being injected every hour. By noon the animal had made a perfect recovery, the mucous membranes of the mouth being a rosy pink (a good criterion of the viability of a liverless dog). At 12.13 p. m. the blood sugar was 0.134 per cent, at 1.25 p. m., 0.100 per cent, at 3.20 p. m., 0.116 per cent, and at 5.26 p. m., 0.113 per cent (the condition of the animal was still excellent). At 8.20 p. m. the dog urinated copiously and appeared normal in every respect. At 9.00 p. m. the blood sugar was 0.116 per cent. At 10.30 p. m. the animal vomited about 30 cc. of material. At 11.50

p m the blood sugar was 0.089 per cent. The animal died at 3:45 a m, on January 7, with typical "second-stage" symptoms. Necropsy revealed nothing of significance to the experiment.

This and similar experiments revealed that the blood sugar level was practically constant after uncomplicated hepatectomy for the first ten hours if the animal received 0.25 Gm of dextrose per hour either continuously or every fifteen minutes, or indeed every hour. In the latter circumstances the blood samples were removed for analysis just prior to the injections. With this information we investigated the blood sugar content of such dehepatized dogs subjected to vigorous muscular contraction, such as, for instance, those induced by an injection of strychnine. A typical protocol follows, which is one of several similar experiments with identical results.

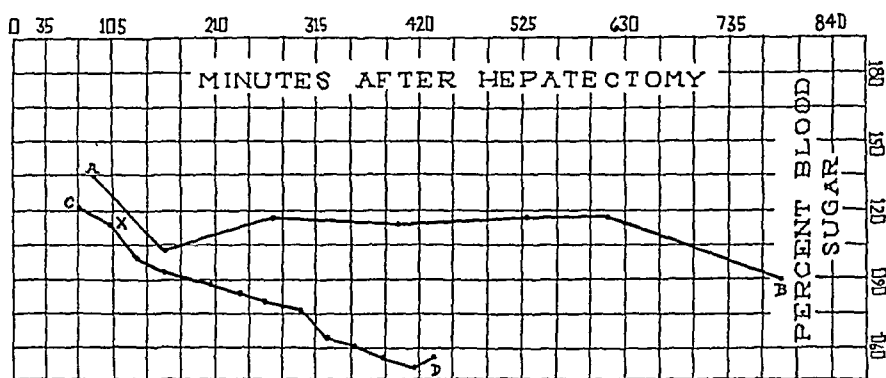


Chart 1—Curve AB indicates the typical level of the blood sugar in a liverless dog receiving a continuous injection of dextrose at the rate of 0.25 Gm per kilogram per hour. Curve CD indicates the typical level of the blood sugar under the same conditions except that the animal was strychninized at X.

### III EFFECT ON BLOOD SUGAR OF STRYCHNINIZED LIVERLESS DOG OF INJECTIONS OF DEXTROSE SOLUTION EVERY FIFTEEN MINUTES AT THE RATE OF 0.25 GM PER KILO GRAM PER HOUR

On Jan 18, 1932, a female dog weighing 11 Kg was dehepatized. The operation was well done. The Eck fistula was completed at 11:10 a m. The liver was removed at 11:20 a m and the last stitch placed in the skin at 11:30 a m. The animal made a sthenic recovery, which was practically complete at 11:45 a m. At that time the animal was given the first injection of 5.5 cc of 12.5 per cent dextrose in saline solution by means of a cannula in a saphenous vein. Injections were given every fifteen minutes. The blood sugar sample was removed from time to time just prior to an injection. At 12:30 p m the blood sugar was 0.120 per cent (chart 1). At 1:00 p m, 1 mg of strychnine sulphate was given intravenously. At 1:03 p m, 0.5 mg was injected. The animal was only mildly hyperexcitable and at 1:06 p m was given an additional 0.25 mg of the drug. At 1:03 p m the blood sugar was 0.113 per cent. At 1:07 p m violent generalized tetanic convulsions developed which persisted until 1:15 p m.



During this time the spasms were sufficiently severe to necessitate artificial respiration. By 1 20 p m the convulsion had subsided completely, but by 1 45 p m the animal was still breathless from the exertion. At 2 00 p m it was still hyperexcitable to tactile stimulation. Meanwhile the blood sugar values were as follows: at 1 30 p m, 0.097 per cent, at 2 00 p m, 0.092 per cent, at 2 45 p m, 0.087 per cent, at 3 15 p m, 0.084 per cent, at 3 45 p m, 0.080 per cent, at 4 15 p m, 0.077 per cent, at 4 45 p m, 0.063 per cent, at 5 14 p m, 0.060 per cent, at 5 44 p m, 0.056 per cent, at 6 14 p m, 0.053 per cent, and at 6 44 p m, 0.056 per cent. This animal was still hyperexcitable by 5 13 p m. (This prolonged hyperexcitability vindicates the contention of Priestley, Mann and one of us [Dr Markowitz]<sup>18</sup> that the liver plays a major rôle in the destruction of strychnine and that the liverless animal is more susceptible to strychnine.) The animal voided large quantities of urine several times during the experiment. At 6 50 p m it was in fair condition and was killed. The observations at necropsy were essentially negative.

In consequence of the Hill-Meyerhoff theory concerning the essential rôle of carbohydrate in the development of muscular tension, it has largely come to be assumed that contracting muscle derives at least a part of its energy from blood sugar. This contention received support from the classic experiments of Locke and Rosenheim,<sup>19</sup> who showed that perfused (nonworking) cardiac muscle consumed dextrose at a rate of approximately 10 mg of dextrose per gram per hour. This was the first indication that living tissue could make use of the simple dextrose molecule to supply its energy requirements. This fact is of historical importance. Minkowski<sup>9</sup> in his work on liverless geese, and Mann and Magath with liverless dogs, showed that the well-being and indeed the life of the organism were affected when the sugar content of the blood was diminished. The experiment just recorded by us is an addition to this information, proving that contracting skeletal muscle withdraws much greater quantities of sugar from the blood than does resting muscle.

It became necessary at this stage of our experiments to determine what were the sugar requirements of depancreatized dogs which were dehepatized in the fully diabetic state. When the liver is extirpated from diabetic animals forty-eight or more hours after pancreatectomy, the blood sugar, as Kausch,<sup>20</sup> Macleod and Pearce and Mann and Magath have shown, shows the usual decline, from which the conclusion is inevitable that diabetic tissues in the resting condition have the normal power of consuming dextrose. Lusk and his pupils have consistently ignored the possibility that the diabetic organism can oxidize

<sup>18</sup> Priestley, J. T., Markowitz, J., and Mann, F. C. *Am J Physiol* **96** 696, 1931.

<sup>19</sup> Locke, F. S., and Rosenheim, O. *J Physiol* **36** 205, 1907.

<sup>20</sup> Kausch, W. *Arch f exper Path u Pharmacol* **39** 219, 1897.

dextrose. Their stand has been based almost entirely on two facts (1) The respiratory quotient of fully diabetic dogs is 0.71 (the theoretical respiratory quotient of fat oxidation), (2) ingested dextrose is quantitatively excreted in the urine. It has been pointed out by several workers that this stand is not worthy of credence. What is called the respiratory quotient is merely a hypothesis. Although none is more appreciative than we are of Lusk's contributions to science, we feel that he is here in error. Diabetic tissue has been shown by a number of workers, including us, to be capable of utilizing considerable quantities of dextrose and we feel that arguments based on such uncertain grounds as the respiratory quotient are not applicable in refuting this fact. It may be argued that part of the decline in blood sugar is due to the urinary excretion of sugar. The following protocol illustrates that diabetic tissue consumes large quantities of dextrose even when there is no possibility of the excretion of dextrose in the urine.

#### IV THE DECLINE OF BLOOD SUGAR FOLLOWING THE REMOVAL OF ALL OF THE ABDOMINAL VISCERA IN THE COMPLETELY DIABETIC DOG

On June 3, 1931, a dog weighing 8 Kg. was completely depancreatized. On June 6 it was in fair condition and weighed 7 Kg. The animal was etherized on this date and the abdominal viscera were completely removed except for the suprarenal glands and the urinary bladder. The operation was accomplished as follows. The two kidneys were first removed. The celiac axis and superior mesenteric artery were tied as they originated from the aorta at the left crus of the diaphragm. The inferior mesenteric artery was then tied, being found traversing the middle of the descending mesocolon. The rectum was clamped and cut, the anal stump being tied with stout packing cord. The root of the mesentery was next cut until the superior mesenteric artery and celiac axis were reached, these being again ligated and cut distal to the ligature. The structures in the lesser omentum were cut between clamps. The lower esophagus was transected between clamps and tied. The alimentary canal was then removed from the abdomen. The liver was removed by tying and cutting the inferior vena cava below and above the liver. The abdomen was packed with moist Turkish towels and the abdominal wall closed with three layers of sutures. Animals usually make a good recovery after such procedures, and walk about after the anesthesia is over. At 9:35 a. m., when the animal was first etherized, the blood sugar was 0.336 per cent. At 10:17 a. m., when the last stitch was placed, the blood sugar was 0.316 per cent. By 10:33 a. m. the animal had completely recovered. At 10:45 a. m. the blood sugar was 0.259 per cent (chart 2). At 11:30 a. m. it was 0.205 per cent, at 12:30 p. m., 0.130 per cent, at 1:30 p. m., 0.063 per cent, and at 2:15 p. m., 0.046 per cent (the animal was barely conscious). At 2:16 p. m. the animal was given 0.5 Gm. of dextrose per kilogram in 25 per cent solution. It improved and was able to stand. At 2:30 p. m. it was killed. Observations at necropsy were essentially negative.

This experiment and similar ones demonstrate that diabetic tissue uses dextrose. At first sight it would appear that the extent of utilization might be normal. To obtain information on this point the effect on the level of the blood sugar was determined when 0.25 Gm of dextrose in solution per hour was injected into liverless dogs which previously had been completely depancreatized.

A few words are necessary concerning the general condition of dogs that are dehepatized in the fully diabetic state. Such animals recover from the hepatectomy well, but in most instances their condition soon becomes poor. At this stage they often have a clinical picture resembling hypoglycemia but when the blood sugar is estimated this is found

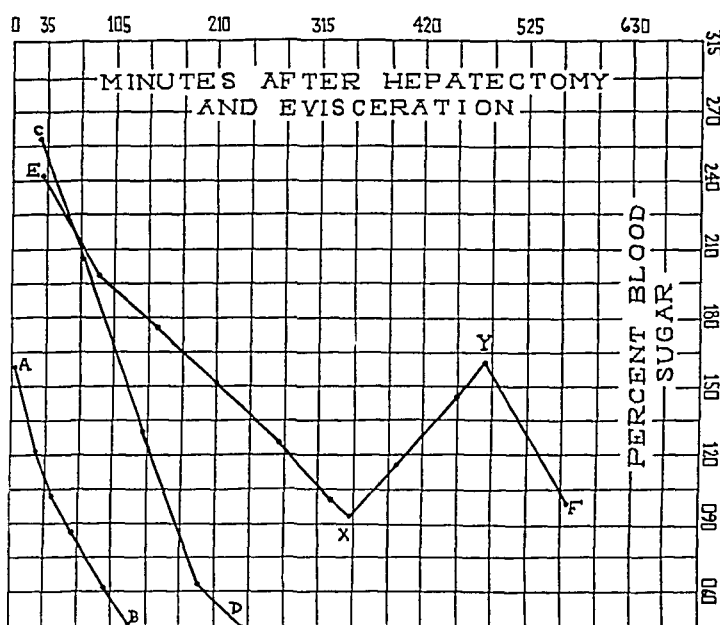


Chart 2—Curve *AB* shows a decline in the blood sugar of a totally eviscerated dog (not mentioned in the text), this is inserted for comparison with curve *CD*. Curve *CD* shows a decline in the blood sugar of a totally eviscerated dog depancreatized four days previously. Note the precipitate decline in blood sugar, in spite of the absence of the kidneys. Curve *EF* shows the decline in blood sugar following hepatectomy in a dog depancreatized three days previously. At *X* the injection of dextrose at the rate of 0.25 Gm per kilogram per hour was started. At *Y* the injection was discontinued. The rapid decline in blood sugar is promptly resumed.

to be over 0.1 per cent. The injection of dextrose effects a transitory recovery, and it is uncertain whether this is due to the dextrose or to the increase of blood volume. In a few cases, however, fully diabetic subjects withstand hepatectomy sufficiently well to be in good condition and fully conscious until typical hypoglycemic blood sugar values are attained. These are the most suitable for studying the extent to which diabetic tissue consumes dextrose. Mann and Magath have drawn

attention to the fact that liveless diabetic dogs usually succumb long before the blood sugar has attained a true hypoglycemic level, there being a transitory restoration to an apparently normal condition following the injection of dextrose. There can be no question, however, that an occasional subject is more viable and lasts to the hypoglycemic level.

We have no explanation to offer for the limited survival period which is the rule following extirpation of the liver in the fully diabetic state. One experiment is reported that was technically flawless and in which the animal survived for ten hours after hepatectomy.

#### V EFFECT ON BLOOD SUGAR OF INJECTING DEXTROSE AT THE RATE OF 0.25 GM PER KILOGRAM PER HOUR IN A PREVIOUSLY DEPANCREATIZED LIVERLESS DOG

On Jan 22, 1932, a dog weighing 15.5 Kg was completely depancreatized. On January 25 it weighed 14 Kg and was dehepatized under ether anesthesia. At operation the liver appeared very fatty, as is usual in diabetes of this duration. The Eck fistula was completed at 10:50 a m and the extirpation at 11:00 a m. A noisy, sthenic recovery soon followed, the animal being normal in appearance by noon. At 11:30 a m the blood sugar was 0.242 per cent (chart 2), at noon, 0.219 per cent, at 12:30 p m, 0.200 per cent, at 1:30 p m, 0.176 per cent, at 2:30 p m, 0.152 per cent, at 3:30 p m, 0.128 per cent, and at 4:30 p m, 0.100 per cent. At 4:45 p m, when the blood sugar was presumably 0.094 per cent, administration of dextrose was begun intravenously at the rate of 0.06 Gm per kilogram every fifteen minutes. At 5:29 p m the blood sugar was 0.116 per cent, at 6:29 p m, 0.144 per cent. Injections of dextrose were given until 7:00 p m and then discontinued. The blood sugar at this stage may be assumed to have been 0.160 per cent. In all, the animal had received 70 cc of 12.5 per cent dextrose between 4:45 and 7:00 p m inclusive. At 7:10 p m it was in excellent condition. At 8:00 p m it was semiconscious and showed some of the symptoms of "second-stage" hepatic insufficiency. At 8:25 p m the blood sugar was 0.097 per cent, and the animal was unconscious. It was now given 0.25 Gm of dextrose per kilogram intravenously. There was practically no improvement. At 9:00 p m the animal, showing typical "second-stage" symptoms, was killed. Necropsy yielded essentially negative results. During the experiment the dog was anuric.

As judged by the initial rate of decline in blood sugar the dextrose consumption of this animal was fully as great as that of the normal dehepatized dog. When the blood sugar had attained a normal value, dextrose was injected at the rate of 0.25 Gm per kilogram per hour over a period of two hours and fifteen minutes, during which time the blood sugar increased from 100 to 160 per cent. On discontinuing the injection it fell, however, in one hour and fifteen minutes to 0.097 per cent. As judged by the effect of the injection, it would appear that the dextrose requirement of a diabetic liveless organism is slightly less than in the nondiabetic state. To keep the blood sugar normal would require 0.19 Gm per kilogram per hour, in our opinion. The difference we believe is due to the fact that nondiabetic liverless dogs are per-

forming a certain amount of muscular exertion which consumes extra dextrose, which is also achieved by the contraction of the heart. This experiment is submitted as evidence, therefore, that the dextrose requirements of resting skeletal muscle are essentially the same in both the diabetic and the nondiabetic states.

The *experimentum crucis* for this hypothesis would be obtained by observing the dextrose tolerance of a diabetic liverless dog subjected to strychnine spasms. This we have not accomplished.

#### COMMENT

On the basis of experiments performed by us on liverless dogs and on heart-lung preparations in both the nondiabetic and the diabetic state, evidence is presented that the dextrose consumption of resting muscle is the same in both the diabetic and the nondiabetic state. During muscular exercise it was demonstrated that the dextrose requirement of normal muscle was increased, whereas in the diabetic state the muscular contraction did not involve an extra consumption of blood sugar. The diabetic state apparently involves a condition in which the dextrose molecule is not available for the machinery responsible for the development of tension in muscle. It would seem that the consumption of carbohydrate by muscle is of two types: (1) In the resting condition the basal requirement of dextrose is the same in both the diabetic and the nondiabetic state, and (2) in the working condition the extra consumption of dextrose is possible only in the nondiabetic state. In other words, the consumption of dextrose by working diabetic muscle is the same as that of resting diabetic muscle.

#### SUMMARY

1 Heart muscle in a normal heart-lung perfusion consumes 4 mg of dextrose per gram per hour, as was previously shown by Knowlton and Starling.

2 Heart muscle in a diabetic heart-lung perfusion consumes less than one-fourth this quantity. This figure corresponds to the requirement of resting skeletal muscle of liverless dogs.

3 The decline in blood sugar following removal of the liver in dogs is the same in both the nondiabetic and the diabetic state.

4 The injection of 0.25 Gm of dextrose intravenously per kilogram per hour in liverless dogs suffices to maintain a normal level of blood sugar, as was previously shown by Mann and Magath.

5 When liverless dogs are subjected to severe strychnine spasms the continuous injection of dextrose at this rate is insufficient to maintain the blood sugar and it falls progressively to a hypoglycemic level in five hours.

6 When diabetic liverless dogs are given intravenous injections of dextrose at the rate of 0.25 Gm per kilogram per hour after the blood sugar has declined to a nondiabetic level there is a slowly progressive rise of the blood sugar level. It is estimated that the blood sugar would be maintained at an approximately normal level by the injection of 0.19 Gm of dextrose per kilogram per hour.

7 On the basis of these experiments and those quoted from the literature the hypothesis is propounded that in the diabetic state the dextrose requirement of resting skeletal muscle is the same as in the nondiabetic state, but that in the diabetic state contracting muscle is unable to utilize the dextrose molecule for the purpose of obtaining the extra energy. Apparently it is a function of insulin to elaborate the dextrose molecule so that it is available for this purpose.

# News and Notes

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## AMERICAN MEDICAL ASSOCIATION

The Eighty-Fourth Annual Session of the American Medical Association will be held in Milwaukee, June 12 to 16. The Registration Bureau and the Scientific and Technical Exhibits will be housed in the Milwaukee Auditorium, and the Opening General Meeting will be held at the Auditorium on Tuesday, June 13, at 8 00 p m. The readers of the ARCHIVES no doubt will be particularly interested in the following sections, which will hold sessions in the Milwaukee Auditorium on Wednesday, Thursday and Friday: Practice of Medicine (mornings), Plankinton Hall, Pathology and Physiology (mornings), North Section of Market Hall, and Pharmacology and Therapeutics (afternoons), North Section of Market Hall.

## AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians will hold its eighteenth annual clinical session in Chicago, with headquarters at the Palmer House, April 16 to 20, 1934. Announcement of these dates is made not only with a view of apprising physicians generally of the meeting, but also to prevent conflicting dates with other societies that are now arranging their 1934 meetings. Dr. George Morris Piersol, of Philadelphia, is president of the American College of Physicians, and will arrange the program of general sessions. Dr. James B. Herrick, emeritus professor of medicine of Rush Medical College, Chicago, has been appointed general chairman of local arrangements and will be in charge of the program of clinics. Mr. E. R. Loveland, the executive secretary, 133-135 South Thirty-Sixth Street, Philadelphia, is in charge of general and business arrangements, and may be addressed concerning any feature of the forthcoming session.

## AMERICAN HEART ASSOCIATION

The scientific session of the American Heart Association will be held on June 13, 1933, from 9 30 to 5 30 p m in the Knickerbocker Hotel, Milwaukee.

## FIRST FRENCH CONGRESS OF THERAPEUTICS

A congress of therapeutics will take place in Paris, October 23 to 25, 1933, under the presidency of Professor Loeper, president of the Society of Therapeutics. Papers will be presented on the following subjects: (1) parenteral treatment of gastric ulcer, (2) medicinal combinations, (3) treatment of colibacillosis, (4) the epinephrines, (5) short waves in therapeutics and (6) treatment of radiodermatitis. The detailed program will be published later, for information apply to M. le Dr. G. Dom, editeur, trésorier du Congrès, 8, place de l'Odeon, Paris, 6e.

## Book Reviews

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**Sex and Internal Secretions** Edited by Edgar Allen With a Foreword by Robert M. Yerkes Price, \$10 Pp 951 Baltimore Williams & Wilkins Company, 1932

This is a book incorporating the results of ten years' research by a group of American investigators, carefully selected by the Committee on Research in Problems of Sex of the Division of Medical Sciences, National Research Council. Specialization in research has attained the point where any detailed authoritative survey requires a group effort. Consequently, the editor has gathered together a group of investigators whose work has established them in their respective fields. The body of the book is divided into nineteen chapters, and each contributor has developed his chapter in his own way, and assumes full responsibility for the content of his section, including his discussion of the work of other investigators.

At the onset it is admitted that a brief definition of the biologic conception of sex is impossible. Not "sex" but sexes are discussed, since there is no such biologic entity as sex. What exists in nature is a dimorphism within species into male and female individuals, which differ with respect to contrasting characteristics, for each of which in any given species is recognized a male and a female form, whether these characteristics are classed as of the biologic, psychologic or social order.

In the earlier chapters the genetics of sex is discussed. Riddle has an excellent contribution on metabolism and sex. Two chapters are then given over to the testis and its hormones. The editor's choice of subject is the "Ovarian Follicular Hormone, Theelin", he discusses the results of its injection into lower animals, its substitutional value in ovariectomized animals, the vaginal reaction, its action on accessory genital organs, its function during pregnancy and its application to human welfare. Allen states that the principal function of theelin is to control the accessory genital organs and that it apparently has little effect on the ovaries themselves. It is a temporary substitute rather than a cure for hypo-ovarian disorders. Doisy, who isolated and crystallized theelin, wrote the chapter on its biochemistry. Hisaw discusses the physiology of the corpus luteum as demonstrated by extracts. Inhibition of the estrous cycle and ovulation, mucification of the vaginal mucosa, relaxation of the pelvic ligaments of the guinea-pig and uterine effects in the nature of motility of the organ and progestational changes of the endometrium are dealt with in a routine manner. Turner devotes a chapter to the mammary glands, in which he deals with the effect of ovarian grafts, mammary growth during pregnancy and the physiology of lactation. The last half of his contribution is given over to experimental development of the mammary glands as influenced by the ovarian and anterior pituitary hormones, either singularly or in combination. The next chapter includes plumage tests on birds that have undergone gonadectomy or have received hormonal injections. Hartman deals with ovulation and the transport and viability of ova and sperm in the female genital tract. Smith discusses the effect of ablation and implantation of the anterior hypophysis on the reproductive system, and the influence of sex, the sex cycle and age on the pituitary content of the gonad-stimulating hormone. Engle's contribution presents the effects of extracts of the anterior pituitary and similar active principles of blood and urine during pregnancy on various animals of both the male and the female sex. In the latter part of the chapter he comments on the placenta as the probable source of the hormone, and the biologic implications favoring the concept of a single gonadokinetic substance in the anterior lobe. These last two authors discuss the effect of the thyroid and suprarenals on genital function. Stone has a chapter on sexual drive, while Pratt, the only contributor



who is a doctor of medicine, deals with the endocrine disorders in sexual function in man, and attempts to present a clinical application of the various hormones to sexual dysfunction

This book deals predominately with a method of control of sex characteristics, which are especially related to vertebrates, mediated by hormones circulating in the blood. It is distinctly not a popular book on "sex," but should appeal to the scientifically minded student of problems of sex and of sexual functions in the lower animals. The internist and gynecologist will probably find many chapters too experimental for their interests, as all the contributors except one are essentially research workers. The bibliography at the end of each chapter offers an extensive field for reference and investigation in the study of the sex hormones.

The face print is monotype, number 31 E, Bruce oldstyle, and is appropriate because it is closely set and legible. The main text is 10 point. The illustrations are excellently displayed on a Cumberland English finish quality of paper, and the binding is in the T pattern of Interlaken extra colors.

**The History of Dermatology** By William Allen Pusey, A M, M D, LL D, Professor of Dermatology (Emeritus), University of Illinois, sometime President of the American Dermatological Association, and of the American Medical Association. Fabrikoid. Price, \$3. Pp 223, with 32 illustrations. Springfield, Ill. Charles C Thomas, 1933.

That Dr. Pusey would write an interesting book was a foregone conclusion, but that he could cover the field so well in such a short work and not have a mere recitation of names, figures and facts is remarkable. The book is divided into two parts.

The first part, of 175 pages, deals with the history of dermatology from the pre-Hellenic age to the present. Ancient, medieval, and early modern dermatology is treated adequately, but most of this part is concerned with the modern phase, after 1800. The early individualistic British are exemplified by Willan and Bateman, then followed the ascendancy of the French school, which grew up about the St. Louis Hospital, which in 1801 became an exclusive dermatologic institution. Alibert, Biett, Gibert, Devergie and Bazin are the outstanding figures delineated. The leadership soon passed to Germany, because there medicine became a part of university organization. While earlier Germans did much excellent work, the contributions of Hebra and Kaposi served to give preeminence to the Vienna school. Scandinavian, Italian, later French (Besnier, Vidal, Hallopeau and Brocq), later English (Wilson, Fox, Hutchinson and Crocker) and Continental (Neisser, Unna and Finsen) contributors receive adequate consideration.

American dermatology is not forgotten. Bulkley, Worchester, James C. White, Piffard, Duhring, Hyde, Hardaway and George Fox form part of the roll of distinguished American dermatologists whom the author mentions. Of more than special interest is the resurrection of an almost forgotten pioneer American dermatologist, Noah Worchester, who in 1845 published a 292 page text on "Diseases of the Skin," the first American book of its sort.

The history is developed mostly by individual biographical sketches. Each sketch, complete in itself, fits into the whole to form a finished picture. The relationship of dermatology to other fields of medicine, syphilology and the founding of societies and journals is also considered.

The second part, of 36 pages, is an alphabetical index of all, rare and common, conditions of the skin with the name and date of the first describer and an easily obtained reference where a bibliography and discussion of the subject may be found. This historical glossary represents an immense amount of bibliographical work condensed into a brief and easily available form. The work was chiefly done by the author's associate, Dr. Herbert Rattner.

The book is well bound, the paper is of good quality, the type is large and easily read, the illustrations are excellent, the proof-reading is good, and the general lay-out is a credit to the publisher.

No dermatologist should be without this book. Students of medical history will find it a short and complete exposition of the growth of dermatology, and general medical readers will enjoy Dr. Pusey's clear and readable style and obtain a background of dermatologic lore not previously obtainable in English. The author and the publishers are to be congratulated.

**Diagnosis and Treatment of Diseases of the Thyroid Gland** By George Crile and Associates. Price, \$6.50. Pp. 491. Philadelphia: W. B. Saunders Company, 1932.

Dr. Crile and twenty-three of his associates have contributed to this volume. It really amounts to a collection of papers on thyroid topics by members of a thyroid clinic. The chapters vary considerably in quality and cannot, when taken collectively, be said to cover in any comprehensive way the field implied by the title. The book as a whole lacks cohesiveness, and there are in it some rather striking lacunae. For example, one finds no adequate discussion of such an important subject as myxedema, either its diagnosis or its treatment. The arrangement of the work is rather trying for the reader who wishes to use it as a textbook. Topics are so scattered that it is hard to find anywhere in one place a full discussion of all the important aspects of either diagnosis or treatment of any of the important diseases of the thyroid.

The chapters on surgery by the elder Crile are the most important in the book. The wisdom acquired by this master surgeon in a colossal operative experience is here set forth with sufficient clarity. When he enters the field of biophysics, however, Dr. Crile becomes somewhat nebulous.

Of other chapters, those which impressed the reviewer most favorably were those of Dinsmore on "Hyperthyroidism in Children," Anderson on "Cardiac Disturbances Associated with Hyperthyroidism," Mullin on "Laryngeal Disturbances in Hyperthyroidism," John on "Carbohydrate Metabolism in Hyperthyroidism" and Nichols on "Roentgenological Observations in Thyroid Disease." It is a pity that this last mentioned excellent chapter does not cover all aspects of roentgenology of the thyroid.

Toward the end of the book is a chapter in which Dr. Crile gives his theories of the relation of the suprarenals to thyrotoxicosis. He claims to have obtained good results in a series of cases of hyperthyroidism by suprarenal denervation, but gives no detailed information by which the reader can evaluate the method for himself.

**Lehrbuch der Histologie und Histogenese** By Dr. Univ. Med. Josef Schaffer, o. o. Professor der Histologie an der Universität in Wien. Third edition. Price, 20 marks. Pp. 576, with 640 figures in the text (some in colors) and 14 additional full page colored plates (mostly lithographs). Leipzig: Wilhelm Engelmann, 1933.

This is a third and completely revised edition of a textbook that has been outstanding during the last twelve years. Several cuts have been replaced by better ones, and more than 70 new ones have been added. The 37 page section on microscopy of earlier editions has been eliminated to make room for new matter necessitated by advances in many lines, especially in the supporting tissues and endocrine organs. Histogenesis is carefully summarized after the adult structure of each tissue or organ has been described. The book is up to date and well illustrated. The type is clear and the paper good. Many composite diagrams, such as changes in the uterine mucosa during the menstrual cycle, are useful features. At the beginning of the book there is a selected list of 74 texts on microscopy, cytology, histology and histologic technique, and at the end is added a bibliography of original papers by about 650 authors.

The topics in the order of presentation in part I are blood, cell division, epithelia (including glands in general), connective and supporting tissues (bone unusually complete) and muscular and nerve tissues (including general sensory and

motor endings) Part II discusses the special histology of the organs in the following order: vascular system and lymphoid organs, endocrine organs (thyroid, parathyroid, hypophysis, suprarenal, pineal, carotid and coccygeal bodies, islands of Langerhans, corpus luteum and interstitial cells of the testis), the skin and its appendages, digestive system, respiratory system, urinary system, male and female sex organs and special sense organs (visual, auditory and olfactory). It is a well balanced summary of microscopic anatomy and should continue to be widely used as a general text wherever the German language is spoken.

**The Colon, Rectum and Anus** By Fred W. Rankin, M.D., J. Arnold Barger, M.D., and Louis A. Buie. Price, \$9.50. Pp. 846, with 435 illustrations. Philadelphia: W. B. Saunders Company, 1932.

This volume is concerned with the diagnosis and treatment of medical and surgical conditions of the large bowel and contains chapters on anatomy and physiology, and embryology of this region. As is to be expected, the greatest portion of the book is devoted to surgery, including operative procedure and choice of the anesthetic. The material presented is obtained from a study of the records of the Mayo Clinic plus a rather comprehensive review of the literature. At the end of each chapter is an excellent bibliography of the subject considered. Statistical data, obtained both from the authors' records and from the literature, are presented with considerable thoroughness.

Of especial interest to the reviewer are the sections on chronic ulcerative colitis and parasitic diseases of the large bowel. In the instance of the former, one is impressed with the idea that the writer feels he is presenting a subject that is going to be read with considerable skepticism, and an intense effort is made to be convincing. As in the past, his ideas as to etiology and treatment of this condition will be accepted with reservation. A great many excellent plates of the gross pathologic changes and a few of microscopic sections are to be found, though none are colored. There are numerous reproductions of x-ray plates of the colon in this chapter, as in practically all others. It seems strange that in considering the diagnosis of chronic ulcerative colitis not one plate of the proctoscopic picture is to be found. This applies to other conditions of the bowel as well, as only three sketchy proctoscopic pictures are found in the entire volume.

The authors are to be commended for the easy style and the well chosen English of the volume. Their ability to condense articles, while still retaining important facts, is amazing.

**The Aetiology of Tuberculosis** Translated from the German of the original paper before the Physiological Society of Berlin, March 24, 1882, by Dr. and Mrs. Max Pinner. With an Introduction by Dr. Allen K. Krause. Cloth. Pp. 48. New York: National Tuberculosis Association.

This classic paper by Dr. Koch, announcing the discovery of the tubercle bacillus, presented before the Physiological Society of Berlin in 1882, is published by the National Tuberculosis Association marking the semicentenary of Koch's epoch-making achievement. The paper itself, recently translated from the German by Dr. and Mrs. Max Pinner, is made far more interesting to the present-day reader by a sympathetic and illuminating introduction by Dr. Allen K. Krause. In the introduction, Krause outlines clearly the status of medical knowledge of half a century ago and reviews the scientific endeavors of Koch leading up to his final conclusions in such manner that the reader grasps the state of mind of the medical world when Koch announced his discovery.

The little volume includes a reproduction of the original article as it appeared in the *Berliner klinische Wochenschrift*, a portrait of Koch and other historic illustrations.

## MECHANISM OF EDEMA OF THE RENAL TYPE

STUDY ON BASIS OF CHANGES IN WATER CONTENT OF BLOOD AND  
IN PROTEIN CONTENT OF BLOOD PLASMA DURING CYCLE  
OF EDEMA IN CHILDREN

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A knowledge of the changes that occur in the water content of the blood during the development and subsidence of edema of the renal type should help to disclose the mechanism of the production of the edema. For example, if the edema is due to an insufficient elimination of water by the kidneys, and this is believed by von Noorden<sup>1</sup> to be a factor at least in some cases, a high content of water in the blood might be expected during the development of edema. If the edema is due to retention of water by the body tissues, as Fischer<sup>2</sup> believes, the water content should presumably be low during the developmental stage (unless one conceives of a concurrent edema of the blood), and should approach a normal or higher than normal level just preceding and during diuresis and loss of edema. Likewise, if Epstein's<sup>3</sup> theory is correct that edema in chronic parenchymatous nephritis is the result of a low osmotic pressure of the blood due to a deficient concentration of protein in the plasma, then the water content of the whole blood should be low during the development of edema and higher just preceding and during subsidence of edema. On the basis of his theory, however, a decrease or an increase of the protein content of the plasma should precede a decrease or an increase in the water content of the blood.

Although considerable work on the concentration of the blood and on blood and plasma volumes in edema of the renal type has been reported, the results are in rather poor agreement. There is a sub-

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From the Otho S. A. Sprague Memorial Institute Laboratory of the Children's Memorial Hospital.

1 von Noorden, C. *Handbuch der Pathologie des Stoffwechsels*, Berlin, A. Hirschwald, 1906, vol. 1, p. 1043.

2 Fischer, M. H. *Oedema*, New York, John Wiley & Sons, 1910.

3 Epstein, A. A. Concerning the Causation of Edema in Chronic Parenchymatous Nephritis. Method for Its Alleviation, *Am J M Sc* **154** 638, 1917.

stantial accumulation of data showing the presence of a low concentration of protein in the plasma in edema of nephrosis and of glomerular nephritis with nephrotic syndrome, and there is a tendency at present to attribute the production of edema to the deficit of plasma protein in these conditions. A good review of the literature on these subjects may be obtained from the writings of Loeb,<sup>4</sup> Van Slyke and co-workers,<sup>5</sup> Lovett,<sup>6</sup> Leiter<sup>7</sup> and Elwyn<sup>8</sup>

Evidence tending to indicate a low content of water in the blood in the early phase of renal edema, especially of the nephrotic type of edema, is furnished by Keller,<sup>9</sup> who found abnormally concentrated blood in the early stage of nephrosis at the time of greatest edema. Similarly, Nonnenbruch,<sup>10</sup> while finding polyemia and hydremia in the majority of cases of renal edema, found the concentration of the blood to be normal or even greater than normal in some cases, particularly in the early phase of nephrotic edema. Both of these workers base their conclusions on changes in erythrocyte counts.

On the other hand, on the basis of erythrocyte counts, Frey<sup>11</sup> stated that hydremia is found in nephrosis, and from refractometric measurements of blood serum, Widal<sup>12</sup> thought that polyemia was a condition leading to edema, and Reiss<sup>13</sup> stated that edematous nephritic patients often have hydiemia. Veil,<sup>14</sup> though he found normal concentrations of water and sodium chloride in the blood in tubular nephritis, believed that a transient hydremia and hyperchloremia occur and are followed

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4 Loeb, Leo. *Edema, Medicine* **2** 171, 1923

5 Van Slyke, D. D., Stillman, E., Moller, E., Ehrlich, W., McIntosh, J. F., Leiter, L., MacKay, E. M., Hannon, R. R., Moore, N. S., and Johnston, C. *Observations on the Courses of Different Types of Bright's Disease, and on the Resultant Changes in Renal Anatomy, Medicine* **9** 257, 1930

6 Lovett, B. R. *The Quantitative Relation of Serum Albumin and Globulin, Arch Path* **4** 984 (Dec.) 1927

7 Leiter, L. *Nephrosis, Medicine* **10** 135, 1931

8 Elwyn, Herman. *Edema and Its Treatment*, New York, The Macmillan Company, 1929

9 Keller, cited by Volhard, F., and Fahr, T. *Die Bright'sche Nierenkrankheit, Klinik Pathologie und Atlas*, Berlin, Julius Springer, 1914, p. 86

10 Nonnenbruch, W. *Ueber extrarenale Oedemgenese und Vorkommen von konzentriertem Blut bei hydropischen Nierenkranken, Deutsches Arch f klin Med* **136** 170, 1921

11 Frey, W. *Die hamatogenen Nierenkrankheiten, Ergebn d inn Med u Kinderh* **19** 422, 1921

12 Widal, F., Benard, R., and Vaucher, E. *L'hydremie chez les brightiques et les cardiaques oedemateux: son etude a l'aide de la methode refractometrique, comparaison de ses variations a celles du poids, Semaine med* **31** 49, 1911

13 Reiss, E. *Die refractometrische Blutuntersuchung und ihre Ergebnisse fur die Physiologie und Pathologie des Menschen, Ergebn d inn Med u Kinderh* **10** 531, 1913

14 Veil, W. H. *Physiologie und Pathologie des Wasseraushaltes, Ergebn d inn Med u Kinderh* **23** 648, 1923

by a rapid disappearance of the excessive water and sodium chloride into the tissues

Cohnheim<sup>15</sup> recognized the frequent occurrence of edema in hydremic patients, but was of the opinion that hydremia is not a cause of edema, and that hydremic plethora is not the cause of generalized edema of the type characteristic of renal disease. Volhard<sup>16</sup> believed that hydremia leads to diuresis, and that if diuresis is impossible the hydremia continues, but that this alone is not sufficient to cause edema. Volhard and Fahr<sup>9</sup> thought that Keller's finding of concentrated blood in the early stage of nephrosis shows that edema is not caused by poor elimination of water by the kidneys, but that poor elimination of water is to be considered a consequence of scarcity of water in the blood. Nonnenbruch<sup>10</sup> agreed with Volhard that the finding of concentrated blood in renal edema indicates an extrarenal cause of the edema, but said that edema of extrarenal origin does not necessarily produce concentrated blood.

The results of the determination of blood and plasma volumes as a means of indicating whether the blood is diluted or concentrated in edema of the renal type also present considerable disagreement. Linder, Lundsgaard, Van Slyke and Stillman,<sup>17</sup> in two cases of glomerulonephritis of the nephrotic type, in one case of acute nephrosis and in one case of chronic nephrosis, in which the blood plasma volume was determined before, during and after disappearance of extensive edema, found the plasma volume to be uninfluenced by the presence of edema or else actually diminished with the anasarca extreme. In two of these cases, a moderate but definite increase in the plasma volume occurred as the edema disappeared. Darrow and Buckman<sup>18</sup> found a diminished plasma volume in three cases of renal edema in children and in one case in an adult. In two of these cases diagnosed as nephrosis, both in children, the plasma volume returned to normal with the disappearance of the edema. Rusznyák<sup>19</sup> found the blood volume diminished, with nor-

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15 Cohnheim, J. Lectures on General Pathology (A Handbook for Practitioners and Students), translated from the second German edition by Alexander B. McKee, London, The New Sydenham Society, 1889-1890, sect. 1, pp. 452 to 460.

16 Volhard, F. Die doppelseitigen hamatogenen Nierenerkrankungen (Bright'sche Krankheit), Berlin, Julius Springer, 1918, p. 100.

17 Linder, G. C., Lundsgaard, C., Van Slyke, D. D., and Stillman, E. Changes in the Volume of Plasma and Absolute Amount of Plasma Protein in Nephritis, *J. Exper. Med.* **39**: 921, 1924.

18 Darrow, D. C., and Buckman, T. E. The Volume of the Blood. II. The Volume of the Blood and Concentration of Crystalloids and Electrolytes in Dehydration and Edema, *Am. J. Dis. Child.* **36**: 248 (Aug.) 1928.

19 Rusznyák, S. Untersuchungen zur Frage der Gesamtblutmenge des Menschen unter normalen und pathologischen Verhältnissen. II. Nierenkrankheiten und Hypertomen, *Deutsches Arch. f. klin. Med.* **158**: 98, 1927.

mal or slightly increased plasma volume, in three cases of acute glomerular nephritis, two of these with edema, and in one case of subacute glomerular nephritis with mild edema. All of these workers determined the blood volume by means of the dye method.

Using an infusion method of determining blood volume, Plesch,<sup>20</sup> in 1909, found the blood volume percentage of body weight less than one half of normal in a case of renal edema of extreme degree. In 1922, with the carbon monoxide method, he found a low blood volume in one case of renal edema, and a blood volume of about normal, which increased as edema subsided, in two other cases. Waterfield,<sup>21</sup> by a carbon monoxide method, determined the blood volume in five adults with renal edema. His results indicated that the blood volume is low with edema at its height, increases as edema disappears, and may fall again if edema subsequently reappears. In cases without anemia, the changes are of the plasma volume only.

On the other hand, Bock<sup>22</sup> found the plasma volume per kilogram of body weight normal and constant in nephritis with edema, and Brown and Rowntree<sup>23</sup> found normal values for plasma and blood volume in cases of renal edema uncomplicated by anemia. The latter authors,<sup>23a</sup> in cases of nephrosis with diminished hemoglobin and cell values, found the blood and plasma volume definitely increased, but stated that there was no good evidence to indicate that a dilution phenomenon had occurred. Bock, and Brown and Rowntree determined the blood volume by a dye method.

The concentration of the proteins in the plasma in edema of the renal type has been the subject of considerable interest and study, especially since Epstein,<sup>3</sup> in 1917, adapted Starling's theory concerning the influence of the serum proteins on the exchange of water between the blood and the tissues, to explain, on the basis of a low protein concentration in the plasma, the production of the noncardiac edema of chronic parenchymatous nephritis. Starling,<sup>24</sup> in 1896, reported experiments which indicate that the osmotic pressure due to the serum protein of the normal blood approximates capillary blood pressure, and suggested that

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20 Plesch, J. Untersuchungen über die Physiologie und Pathologie der Blutmenge, *Ztschr f klin Med* **93** 241, 1922, Hamodynamische Studien, *Ztschr f exper Path u Therap* **6** 380, 1909.

21 Waterfield, R. L. Changes in Blood Volume in Patients with Edema of Renal Origin, *J Clin Investigation* **9** 589, 1931.

22 Bock, A. V. The Constancy of the Volume of the Blood Plasma, *Arch Int Med* **27** 83 (Jan) 1921.

23 (a) Brown, G. E., and Rowntree, L. G. Blood Volume in Edema of Glomerular Nephritis and Nephrosis, *Arch Int Med* **41** 44 (Jan) 1928, (b) The Volume and Composition of the Blood and the Changes Incident to Diuresis in Cases of Edema, *ibid* **35** 129 (Jan) 1925.

24 Starling, E. H. On the Absorption of Fluids from Connective Tissue Spaces, *J Physiol* **19** 312, 1895-1896.

this osmotic pressure tends to counteract the capillary pressure, thus maintaining a balance between filtration of fluids from the blood vessels into the tissues and absorption of fluids from the tissues into the blood.

There are many reports of the finding of a low concentration of protein in the serum and plasma in edema of the renal type. Bright,<sup>25</sup> in 1827, referred to the finding by Bostock of low serum protein in patients with heavy proteinuria, and, in 1831, to Babbington's finding of 5 per cent of albumin in the serum of a patient with albuminuria and anasarca of two years' standing. Csáthy,<sup>26</sup> in 1891, noted that the serum albumin was more affected than the globulin, which sometimes caused the albumin-globulin ratio to fall below 1, and Erben,<sup>27</sup> in 1905, emphasized the presence of a low or reversed albumin-globulin ratio in parenchymatous nephritis. Epstein,<sup>28</sup> in 1912, by chemical methods, found a low total serum protein with a very low albumin-globulin ratio in two patients with parenchymatous nephritis, and in subsequent papers he has emphasized the presence of a low serum protein in active nephrosis.

The presence of a low concentration of protein in the serum and plasma in the nephrotic type of edema has been confirmed by many workers, including Kollert,<sup>29</sup> Linder, Lundsgaard and Van Slyke,<sup>30</sup> Fahr and Swanson,<sup>31</sup> Moore and Van Slyke,<sup>32</sup> Van Slyke and associates,<sup>5</sup> Clausen,<sup>33</sup> Fodor and Fischer,<sup>34</sup> Peters and associates,<sup>35</sup>

25 Bright, Richard. Reports of Medical Cases, London, Longman, 1827-1831, vols 1 and 2.

26 Csáthy, A. Ueber Globulinurie, *Deutsches Arch f klin Med* **48** 358, 1891.

27 Erben, F. Studien uber Nephritis, *Ztschr f klin Med* **57** 39, 1905.

28 Epstein, A. A. A Contribution to the Study of the Chemistry of Blood Serum, *J Exper Med* **16** 719, 1912.

29 Kollert, V. Ueber das Wesen der Nephrosen, *Ztschr f klin Med* **97** 287, 1923.

30 Linder, G. C., Lundsgaard, C., and Van Slyke, D. D. The Concentration of the Plasma Protein in Nephritis, *J Exper Med* **39** 887, 1924.

31 Fahr, G., and Swanson, W. W. The Quantities of Serum, Albumin, Globulin, and Fibrinogen in the Blood Plasma in Acute and Chronic Nephropathies, *Arch Int Med* **38** 510 (Dec) 1926.

32 Moore, N. S., and Van Slyke, D. D. The Relationships Between Plasma Specific Gravity, Plasma Protein Content, and Edema in Nephritis, *J Clin Investigation* **8** 337, 1930.

33 Clausen, S. W. Parenchymatous Nephritis. I As a General Systemic Disease, *Am J Dis Child* **29** 581 (May) 1925, II Infection of Paranasal Sinuses as Etiology, *ibid* **29** 587 (May) 1925, III The Surface Tension of the Blood Serum, *ibid* **29** 594 (May) 1925.

34 Fodor, A., and Fischer, G. H. Chemische und kolloidchemische Untersuchung des Blutserums und der Oedemflussigkeit bei Oedematosen. I Beitrag zur Theorie des Oedems, *Ztschr f d ges exper Med* **29** 465, 1922.

35 Peters, J. P., Bruckman, F. S., Eisenman, A. J., Hald, P. N., and Wakeman, A. M. The Plasma Proteins in Relation to Blood Hydration. IV Serum Proteins in Nephritic Edema, *J Clin Investigation* **10** 941, 1931.



Schwarz and Kohn,<sup>36</sup> Blackfan and Hamilton,<sup>37</sup> Calvin and Goldbeig,<sup>38</sup> Schlutz, Swanson and Ziegler,<sup>39</sup> and Wolbach and Blackfan<sup>40</sup> The last five studies were principally in children In most instances, when albumin and globulin were determined separately, the decrease in total protein was due to a decrease in albumin, and not infrequently the globulins were increased Kollert<sup>29</sup> pointed out the high fibrinogen content in the plasma of nephrotic patients

Clausen,<sup>33</sup> from the determinations of the serum proteins in nine cases of parenchymatous nephritis, concluded that edema in parenchymatous nephritis is correlated with low serum protein

Peters and his associates<sup>35</sup> determined the total proteins of the serum one hundred and seventy-nine times in twenty-one patients with nephrosis or nephrotic types of nephritis and the albumin and globulin fractions separately in one hundred and eighteen instances in fifteen patients They found edema almost invariably present when the total serum protein was below 4 per cent, but in only three instances, in two patients with circulatory failure, when the total protein was above 5 per cent Edema was found in every instance when the serum albumin was below 2 per cent, and in only one instance (in a case of heart block) when it exceeded 2.75 per cent They stated that with the total protein of the serum between 4 and 5 per cent, edema can usually be eliminated by proper treatment, but that when it is below 4 per cent treatment is usually ineffectual

Barker and Kirk<sup>41</sup> found that when the serum albumin in nephritic patients fell to about 1 per cent, edema appeared, and that it decreased shortly after the albumin increased above 1 per cent

Govaerts<sup>42</sup> found the osmotic pressure of the serum protein low

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36 Schwarz, H., and Kohn, J. L. Studies of Nephritis in Children. I. Nephrosis, *Am J Dis Child* **24** 125 (Aug) 1922

37 Blackfan, K. D., and Hamilton, B. A Study of the Inorganic Constituents of the Serum in Children with Acute Nephritis, *Bull Johns Hopkins Hosp* **41** 322, 1927

38 Calvin, J. K., and Goldberg, A. H. Plasma Proteins and Edema. Their Relationship in a Group of Children Presenting the Nephrotic Syndrome. *Am J Dis Child* **42** 314 (Aug) 1931

39 Schlutz, F. W., Swanson, W. W., and Ziegler, M. R. The Distribution of the Globulin and Albumin Fractions in the Blood and in the Urine in Nephrosis, *Am J Dis Child* **36** 756 (Oct) 1928

40 Wolbach, S. B., and Blackfan, K. D. Clinical and Pathological Studies on So-Called Tubular Nephritis (Nephrosis), *Am J M Sc* **180** 453 (Oct) 1930

41 Barker, M. H., and Kirk, E. J. Experimental Edema (Nephrosis) in Dogs in Relation to Edema of Renal Origin in Patients, *Arch Int Med* **45** 319 (March) 1930

42 (a) Govaerts, P. Influence du rapport albumines-globulines sur la pression osmotique des proteines du serum, *Comp rend Soc de biol* **93** 441, 1925, (b) Influence de la teneur du serum en albumines et en globulines sur la pression osmotique des proteines et sur la formation des oedemes, *Bull de l'Acad roy de med de Belgique* **7** 356, 1927

in nephritic patients with edema. His investigations showed that the albumin fraction exerts approximately four times as great osmotic pressure per gram as the globulin, and that a direct relationship exists between serum osmotic pressures and albumin-globulin ratios.

While the association of a low concentration of the plasma protein with edema of the nephrotic type has been reported by many investigators, some of these have also reported observations which do not seem in keeping with the theory that the formation of the edema is the result of the low concentration of the plasma protein. Schwarz and Kohn,<sup>36</sup> in discussing the cause of edema in nephrosis, referred to a child with a general anasarca and with serum protein of 4.2 per cent who lost 29 pounds (13.2 Kg.) of weight within a week, with disappearance of all manifest edema without change in the blood protein concentration, and said: "It would not appear, therefore, that the reduction in the protein content of the blood is a great factor." Linde, Lundsgaard and Van Slyke<sup>30</sup> stated that with disappearance of edema in their cases the plasma protein concentration was usually increased, but that this was not constant, and concentrations of 4.5 per cent or less were compatible with persistent absence of edema. In discussing the hypothesis that the edema of nephritis is the result of decreased osmotic pressure of the plasma due to low concentration of protein, these authors said: "If this were true it is probable that the lowest protein concentration in the plasma would be found during the stage of increasing and fully developed edema and that the first sign of a change for the better would be a rise in the osmotic pressure consequent upon an increase in the plasma protein," and that in the results reported by them, "no such close relationship appears." Fahri and Swanson<sup>31</sup> are inclined to believe that though a reduction in the plasma protein tends to slow up the output of water somewhat, it is only a minor factor in the formation of edema. In one of their cases of chronic nephrosis with total plasma proteins of 75 per cent and albumin less than 50 per cent of mean normal, the patient excreted 1,350 cc. of urine in four hours after a fluid intake of 1,500 cc. In several cases of glomerulonephritis, a low plasma protein with markedly low albumin fraction was present when diuresis had set in and edema had disappeared. Moore and Van Slyke<sup>32</sup> studied the relationship of the plasma protein concentration to the presence or absence of edema in seventy-five cases of nephritis, and said: "the main and constant factor in producing the tendency toward non-cardiac edema in nephritis is plasma protein deficit." Yet, they pointed out that this is not the only factor in determining the occurrence and degree of edema. They stated that patients with low plasma protein may become comparatively, and sometimes entirely, edema-free on a salt-free regimen, and referred to "an unknown physiological factor which in cases where occurrence or non-occurrence of edema is in the balance, may determine whether edema will occur or not." Van

Slyke and associates<sup>5</sup> found that the tendency to noncardiac edema in nephritis (except in the first weeks of acute nephritis) and in nephrosis approximately paralleled the fall in albumin content of the plasma. They expressed the belief that there are other factors, however, which may resist or reenforce the hydropigenous effect of a deficit of plasma protein, and that with plasma proteins near the level at which their deficit usually produces edema these other modifying factors may cause edema to appear or disappear. They mentioned salt intake as such a factor, and said that with the tendency to edema barely under control, it may appear after infection or operation, and that in some instances fever and in others vomiting seem to make it disappear. Calvin and Goldberg<sup>38</sup> said that edema often appears and disappears more rapidly than do the changes in the blood proteins, and expressed the belief that while the low serum albumin is an important underlying predisposing factor, it cannot entirely account for the sudden changes in the edema, and that the relationship is not a simple one of cause and effect. They refer to some "trigger" mechanism which suddenly causes retention of water, or diuresis, resulting in the typical "cyclic" edema of the nephrotic syndrome in children.

The lack of agreement regarding the water content of the blood in edema of the renal type and the importance of this knowledge to the theories of the cause of the edema make further study on this subject seem worth while. It seems especially desirable to have more information on the changes of the water content of the blood coincident with changes in the course of the edema. We have tried, therefore, to obtain data through the complete cycle of attacks of edema and, especially, at short intervals when the edema was changing from one phase to another.

Although we made no determinations of the absolute volume of plasma or blood, our data on changes in the relative volume of plasma, when considered in relation to the red blood cell and hemoglobin values, and the figures for the total blood solids seem to justify the drawing of conclusions concerning changes in the absolute volume of the plasma. This is especially true of nephrosis, in which rapidly progressing anemia is uncommon and the absolute volume of cells, therefore, is not subject to rapid change from that cause.

The coincidence of edema of the nephrotic type and a low concentration of protein in the plasma, mainly due to decrease in the albumin fraction, is established beyond reasonable doubt by published data. That the low protein concentration in the plasma is the cause of the edema is yet to be proved.

We have attempted to secure further data on whether or not, in the individual patient, decrease and increase in the plasma protein concentration precede respectively increase and decrease, or appearance and disappearance, of the edema with sufficient regularity to indicate a cause and effect relationship. It was thought, also, that a study of the

relation of changes in the concentration of protein in the plasma to changes in the water content of the blood during the cycle of edema might furnish information concerning the influence of plasma protein concentration on the movement of water between the blood stream and the tissues, such as might be expected from consideration of the effect of the proteins on osmotic pressure, if the concentration of proteins in the plasma is important to the development and subsidence of edema

#### PROCEDURE AND METHODS

Blood was taken from an antecubital vein at about 10 30 a m, approximately three hours after breakfast Care was taken to prevent, so far as possible, prolonged stasis <sup>43</sup>

In each case, when practicable, the whole blood solids, the relative volumes of cells and plasma, the specific gravity and viscosity of whole blood, the hemoglobin content, the number of red blood cells and the percentage of the protein in the plasma, and in some cases, of the plasma fibrinogen, globulin and albumin, separately, were determined The nonprotein nitrogen and cholesterol content of the blood were determined as aids to diagnosis

Total solids of whole blood and of plasma were determined in duplicate by the method described by Myers <sup>44</sup> In the case of plasma solids, a correction was made for the sodium oxalate that had been added to the blood to prevent coagulation With few exceptions, the duplicates checked within 0.2 on the percentages of the total solids in the whole blood and in the plasma figure

Plasma proteins, total and fractional, were determined in case 1, and in a few isolated determinations recorded in chart 9, by the method of Wu <sup>45</sup> In all the other cases, the method described by Hawk and Bergeim <sup>46</sup> was used This combines the method of Howe <sup>47</sup> for the separation of the globulins from the albumin, and the separation of the fibrinogen from the other proteins, with the

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43 The observations of Rowe (*a*, The Effect of Venous Stasis on the Proteins of Human Blood Serum, *J Lab & Clin Med* **1** 485, 1915-1916), Peters, Eisenman and Bulger (*b*, The Plasma Proteins in Relation to Blood Hydration in Normal Individuals and in Miscellaneous Conditions, *J Clin Investigation* **1** 435, 1925) and Plass and Rourke (*c*, The Effect of Venous Stasis on the Proteins of Blood Plasma and on the Rate of Sedimentation of the Red Blood Corpuscles, *J Lab & Clin Med* **12** 735, 1927) indicate that venous stasis of five minutes' duration or more may cause a considerable increase in the relative cell volume and red blood cell count, and in the hemoglobin and plasma protein concentrations It seems possible that these effects of stasis may be even greater in cases of renal edema with low plasma protein concentration

44 Myers, Victor C Practical Chemical Analysis of Blood, ed 2, St Louis, C V Mosby Company, 1924, p 160

45 Wu, H A New Colorimetric Method for the Determination of Plasma Proteins, *J Biol Chem* **51** 33, 1922

46 Hawk, P B, and Bergeim, O Practical Physiological Chemistry, ed 9, Philadelphia, P Blakiston's Son & Co, 1927

47 Howe, P E The Use of Sodium Sulphate as the Globulin Precipitant in the Determination of Proteins in the Blood, *J Biol Chem* **49**:93, 1921, The Determination of Proteins in Blood—A Micro Method, *ibid* **49**:109, 1921

method of Koch and McMeekin<sup>48</sup> for the nitrogen determination. The plasma used for these determinations was obtained from blood oxalated in the concentration of from 30 to 50 mg of sodium oxalate per 10 cc of blood. Because of the cell shrinkage and consequent increase in relative plasma volume brought about by the hypertonicity in the blood specimens, our figures for protein must be considered to be slightly lower than their absolute values, and since the oxalation was not carried out in a perfectly constant concentration, it must also be considered that in successive protein determinations in a given case there may be relative errors to the extreme (rarely, though possibly) of 0.3 in the figures for the percentage of total protein in the plasma.

Nonprotein nitrogen was determined by the method of Folin and Wu<sup>49</sup> with the Haden<sup>50</sup> modification for preparing the protein-free filtrate.

Cholesterol was determined in the earlier cases (cases 1, 2, 3-I, 3-II, 5, 6 and 7) by the method of Bloor<sup>51</sup>. The last three determinations in case 3-II and all determinations in case 4 were made by the method of Leiboff<sup>52</sup>.

Specific gravity was determined with bottles of the Gay-Lussac type of 1 cc capacity. Control experiments done with water with a procedure like that used for the blood indicated that our average error in the figure for specific gravity should be considered as 0.001.

Viscosity was determined with a Hess<sup>53</sup> viscosimeter. The method is fully described by Austrian<sup>54</sup>.

Relative cell and plasma volumes were determined in duplicate by a method similar to that employed by Capps<sup>55</sup>. Duplicate tubes of about 0.5 mm bore and about 5 cm length, graduated in hundredths, were filled with the fresh blood, without any anticoagulant, and were immediately centrifugated at a minimum speed of 10,000 revolutions per minute, for five minutes. The percentages were read, and then centrifugation was continued for two minutes longer, and readings made again. Usually the readings were constant, but if there was any change at the second reading, the centrifugation was again continued for two minutes. The duplicate readings of the relative cell volume in percentage of blood checked each other within 2 and most often within 1. Three control experiments were done, one on human blood and two on sheep's blood, to compare the readings on fresh blood

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48 Koch, F. C., and McMeekin, T. L. A New Direct Nesslerization Micro-Kjeldahl Method and a Modification of the Nessler-Folin Reagent for Ammonia, *J Am Chem Soc* **46** 2066, 1924.

49 Folin, O., and Wu, H. A System of Blood Analysis, *J Biol Chem* **38** 81, 1919.

50 Haden, R. L. A Modification of the Folin-Wu Method for Making Protein-Free Blood Filtrate, *J Biol Chem* **56** 469, 1923.

51 Bloor, W. R. The Determination of Cholesterol in Blood, *J Biol Chem* **24** 227, 1916, *ibid* **29** 437, 1917.

52 Leiboff, S. L. A Simplified Method for Cholesterol Determination in Blood, *J Biol Chem* **61** 177, 1924, Modifications in the Method for the Determination of Cholesterol in Blood, *J Lab & Clin Med* **15** 776, 1930.

53 Hess, W. Die Viskosität des Blutes bei Gesunden, *Deutsches Arch f klin Med* **94** 404, 1908.

54 Austrian, C. R. The Viscosity of the Blood in Health and Disease, *Bull Johns Hopkins Hosp* **22** 9, 1911.

55 Capps, J. A. A Study of Volume Index. Observations upon the Volume of Erythrocytes in Various Disease Conditions, *J M Research* **5** 367, 1903-1904.

with those on the same specimen heparinized. In every experiment the value for cell volume in the heparinized sample was found to be less than 1 lower than the value in the fresh sample. This would indicate that any error due to coagulation, in our method, may be considered to be included in an average error of 1 for the relative volume of the cells or of the plasma expressed in percentage of the whole blood.

Hemoglobin was determined in the earlier cases (1, 2, 3-I, 5, 6 and 7) by the acid hematin method of Haden<sup>56</sup>. The standard acid hematin solution was made by the oxygen capacity method of Van Slyke and Stadie<sup>57</sup>. In the later cases (3-II and 4), the Newcomer<sup>58</sup> method was used. The glass disk used was standardized by the Bausch and Lomb Optical Company and released by them in February, 1930.

Single specimens of urine, taken at the time of the withdrawal of specimens of blood, were examined for albumin, blood cells and casts. Records of the daily (12 midnight to 12 midnight) quantity of fluids taken and urine excreted were kept by the nursing staff. Daily weights of the patients at about 8:30 a. m., the degree of pitting of the arm and leg and the results of the intradermal salt solution test<sup>59</sup> were recorded as evidence of the degree of edema and its course.

As might be expected, it was exceptional that a patient was under observation at the onset of the edema, and in the two instances in which this occurred the exact point of the beginning of the edema was not sharply defined. Likewise, it was usually impossible to determine the exact point of disappearance of the last trace of edema, a slight or questionable pitting on pressure over the shin frequently persisted for some time after diuresis seemed to have ended. The intradermal salt solution test was helpful at times in arriving at a conclusion concerning the state of the edema in such instances. On the other hand, the onset of diuresis was in most instances rather well defined and seemed to us an unmistakable sign that the factor or factors responsible for the development, or at least the continuance, of the edema were no longer active or were rendered ineffective by a new factor. A somewhat less definite but earlier evidence of improvement in some of our cases was the lessening of edema of the arm, as shown by lessening of pitting and lengthening of the disappearance time for intradermally injected salt solution in that region. This was seen on several occasions in the stationary phase of edema preceding diuresis.

#### CLINICAL MATERIAL

This report includes data from six patients with renal edema, each studied in both the advancing and the subsiding phase of an acute

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56 Haden, R. L. A Method for the Determination of Hemoglobin, *J. Lab. & Clin. Med.* **8** 411, 1922-1923.

57 Van Slyke, D. D., and Stadie, W. C. The Determination of the Gases of the Blood, *J. Biol. Chem.* **49** 1, 1921.

58 Newcomer, H. S. Absorption Spectra of Acid Hematin, Oxyhemoglobin, and Carbon Monoxide Hemoglobin. A New Hemoglobinometer, *J. Biol. Chem.* **37** 465, 1919.

59 McClure, W. B., and Aldrich, C. A. Time Required for Disappearance of Intradermally Injected Salt Solution, *J. A. M. A.* **81** 293 (July 28) 1923. Aldrich, C. A., and McClure, W. B. The Intradermal Salt Solution Test. II. Its Prognostic Value in Nephritis with Generalized Edema, *J. A. M. A.* **82** 1425 (May 3) 1924.

attack of edema, and from one patient (case 7) studied only during a rather irregularly subsiding phase<sup>60</sup>

For one patient the data from two attacks of edema (cases 3 I and 3 II) are presented. So far as could be judged, there was no anemia in any case at the time of the first determination. Data from sixteen additional cases of renal edema, not presented in detail because they were not

*Data on*

No	Date	Age, Years	Sex	Diagnosis and Condition at Time of Test	Urine, Single Specimen about 11 a m						
					Microscopic Low Power Field						Casts
					Centrifugated			Uncentrifugated			
					Albumin	Red Blood Cells	White Blood Cells	Red Blood Cells	White Blood Cells		
1	3/28/28	11 9/12	F	Deformities of legs resulting from poliomyelitis 10½ years before, otherwise considered to be normal	Trace	0	Innum- erable	Occa- sional granular	0	46	0
2	4/26/29	9 5/12	M	Deformity of right leg result- ing from poliomyelitis 7 years before, otherwise con- sidered to be normal	0	0	0	0	0	0	0
3	12/3 28	9 2/12	F	Congenital dislocation of left hip, otherwise considered to be normal	0	0	50 100	0	0	5 10	0
4	1/14/29	8 8/12	F	Congenital dislocation of both hips, now not in cast, otherwise considered to be normal	0	0	Occa- sional	0	0	0	0
	2/ 4/29	8 8/12			0	0	30 50	0	0	Occa- sional	0
5	7/ 5/29	8 2/12	F	Partial paralysis of both legs resulting from polio- myelitis about 5 years be- fore otherwise considered to be normal	0	0	30 40	0	0	3 5	0
6	4/ 8/29	7 8/12	M	Congenital absence of right fibula, otherwise considered to be normal	0	0	5 10	0	0	0	0
	5/13/29	7 9/12			0	Rare	Occa- sional	0	0	0	0
7	5/27/29	4 6/12	F	Birth paralysis of left arm (Erbs), otherwise considered to be normal	Trace	0	150 200	0	0	5 10	0

Average

Number of determinations  
Number of cases

Normal cases from literature

\* Globulin does not include fibrinogen

60 A brief report including data from six of these cases was presented before the American Pediatric Society in April, 1931, and a summary published in the Transactions of that society. McClure, W. B., de Takats, C. B., and Hinman, W. F. Changes in the Water Content of the Blood During the Course of Edema of Renal Type in Seven Children, *Am J Dis Child* 42:725 (Sept.) 1931, *Tr Am Pediat Soc* 43:62, 1931.

studied in both the advancing and the subsiding phases of edema, or because of the presence of marked anemia, are included in chart 9, which shows the relation between the concentration of protein in the plasma and the degree of edema. Data from seven control cases are presented in the table.

In three of the seven cases with edema which are presented in detail,

### Control Cases

Intradermal Salt Solution Test				Total Solids																Plasma Proteins, Gm per 100 Cc				Whole Blood	
Disappearance Time, Minutes		Pitting		Relative Cell, per Cent by Volume	Hemoglobin, Gm per 100 Cc	Red Blood Cells, Millions	Whole Blood Specific Gravity	Whole Blood Viscosity	Per Cent of Whole Blood	Per Cent of Plasma	Total	Globulin*	Albumin	Fibrinogen	Cholesterol, Mg per 100 Cc	Nonprotein Nitrogen, Mg per 100 Cc									
Arm	Leg	Arm	Leg																						
60+	—	0	—	—	15.0	5.00	—	4.4	20.0	—	—	—	—	—	—	25.0									
60+	60+	0	±	37.0	13.7	5.26	1.049	3.7	18.7	8.45	7.75	2.3	5.05	0.4	250	29.0									
60+	60+	0	0	42.5	12.0	5.46	1.071	4.0	19.6	8.45	6.6	—	—	—	220	30.0									
60+	60+	0	0	37.5	10.9	4.97	—	3.85	19.2	8.7	6.95	—	—	—	230	30.0									
60+	60+	0	0	36.5	11.3	5.38	1.054	3.85	19.0	8.65	7.4	—	—	—	—	28.5									
60+	—	0	±	39.5	13.7	5.25	1.056	3.7	19.1	8.4	8.0	—	—	—	230	25.0									
60+	60+	0	0	39.0	12.5	—	1.055	3.8	18.85	8.2	7.7	2.3	4.9	0.5	230	30.0									
60+	60+	0	0	40.0	12.9	5.56	1.051	3.55	18.8	8.0	6.9	—	—	—	190	28.0									
—	60+	0	0	39.0	13.8	4.61	1.052	3.75	19.6	8.35	6.8	1.7	4.75	0.35	220	30.5									
				38.9	12.9	5.18	1.0526	3.84	19.0	8.4	7.26	2.1	4.9	0.41	224	29.1									
				8.6	9.7	8.7	7.6	9.7	9.7	8.6	8.6	3.3	3.3	3.3	7.6	9.7									
				36.5	12.6 to 14.7	5.06	1.0518	3.9	18.95	8.2	7.07	2.22	4.54	0.3	220	25.35									

the condition was diagnosed nephrosis, in one of these there was an associated Hodgkin's disease, in which the diagnosis was confirmed at autopsy. In the remaining four of the seven cases, the condition was diagnosed glomerular nephritis with nephrotic syndrome. The seven patients had in common edema, albuminuria, high blood cholesterol and low plasma protein. The nonprotein nitrogen of the blood was not



above normal at any examination in the cases of nephrosis but a little above normal on several examinations in two cases of glomerular nephritis with nephrotic syndrome. The blood pressure was 115 mm of mercury at one reading in the case of nephrosis with Hodgkin's disease but normal in the other two cases of nephrosis, it was distinctly above normal in two cases of glomerular nephritis with the nephrotic syndrome. The cases of glomerular nephritis with nephrotic syndrome were differentiated from those of nephrosis particularly on the basis of the finding of more than an occasional red blood cell in the urine.

The drugs administered that might possibly have shortened the course of the edema and brought about diuresis were as follows. In case 2, thyroxin was given from October 13 to November 2 over a period preceding and during diuresis, magnesium sulphate was given throughout the period of study in case 1, from December 5 to December 6 in case 3-II, and irregularly, but only after diuresis had already begun, in case 7.

There was a febrile attack in case 4 during the first three days of diuresis.

At the time of the onset of diuresis, a general diet was being given in cases 1, 2, 5 and 6 (started in case 1, however, only two days before diuresis following a period of low protein, salt-poor diet), low protein, salt-poor diet in case 3-I, low protein, high vitamin, salt-poor diet in case 3-III, high protein, high vitamin diet in case 4, and milk, carbohydrate, salt-poor diet in case 7.

#### EXCERPTS FROM CLINICAL RECORDS

##### CASE 1—*Nephrosis*

A girl, aged 4 years and 7 months, who was admitted to the hospital on May 8, 1928, had been well until one week before, when puffiness of the eyelids was noticed. Swelling rapidly involved both legs and the sacral region, and the abdomen began to enlarge. During this period she drank a great deal of water, but urinated infrequently and in small quantities. The urine at times was thick and dark. On examination, May 9, there was tonsillitis with an exudate, and a puffy face with swelling of the eyelids and of the arms, legs and abdominal wall. This general edema felt rather firm. There was some movable dullness in the abdomen. The temperature was 99.2 F<sup>61</sup> on admission and remained within normal range during the period of study. Systolic blood pressure ranged from 72 to 104 mm of mercury. During our study, cholesterol ranged from 400 to 480 mg, and non-protein nitrogen from 29 to 33.5 mg per hundred cubic centimeters of blood.

On May 8, a low protein, salt-poor diet<sup>62</sup> was begun, after May 17, a general diet was given. Water was not restricted.

<sup>61</sup> Rectal temperature.

<sup>62</sup> Salt-poor diet means food with salt-free butter and with no salt added in cooking or in serving.

Magnesium sulphate was administered from May 9 to June 1

The child, improved, went home against advice on June 5 A trace of albumin was found in the urine two days before

CASE 2—*Hodgkin's Disease with Nephrosis*

A boy, aged 6 years and 9 months, was admitted to the hospital on Sept 13, 1928 He had been admitted in March, 1926, with a diagnosis of Hodgkin's disease He came to the hospital the second time because of a sudden appearance of edema, five days previously, involving the neck, lower extremities and scrotum During the stay in the hospital in 1926, the urine, on one examination contained albumin 1 plus, with no casts and no red blood cells Examination on Sept 13, 1928, showed, besides the glandular enlargement of Hodgkin's disease, edema with slight redness of the abdominal wall, edema of the scrotum and moderate edema of the legs On September 15, there was a general edema, especially marked in the right leg, also in the face and scrotum This edema did not pit easily

The urine on September 22 showed no albumin, on September 24, the albumin was 1 plus, and on October 3, 4 plus

The systolic blood pressure was 115 mm of mercury on September 17 During our study, cholesterol was 380, 310, 390, 380, 310 and 250 mg, and non-protein nitrogen from 27 to 35 mg, per hundred cubic centimeters of blood

The temperature on admission was over 105 F, <sup>61</sup> it rose above 102 F on September 14, was 103 F on September 15, became normal on September 16, and continued within normal range until October 1 During October it fluctuated between normal and 100.5 F, during November it was around 99 and occasionally above 100 F

On September 13, a general diet was given, on September 14, a light diet, and on September 17, a general diet Water was not restricted

On October 13, the administration of thyroxin was begun, it was discontinued on November 2

The child was admitted to the hospital subsequently on May 13, 1929, for recurrence of general edema four days previously The urine showed albumin 4 plus Death occurred on May 17, 1930 Postmortem examination confirmed the diagnosis of nephrosis and Hodgkin's disease

CASE 3-I—*Chronic Glomerular Nephritis with Nephrotic Syndrome*

A boy, aged 5 years and 4 months, was admitted to the hospital for the third time on Feb 21, 1929 He had first been admitted on Oct 4, 1927, with general edema and marked albuminuria, he had been admitted a second time on Nov 6, 1928, for increasing albuminuria Since being discharged from the hospital on Nov 13, 1928, albumin had been found in the urine on every visit to the outpatient department Three days before the present admission the child had had a cold The urine was reddish on the morning of admission The boy had seemed drowsy and had had a little headache

On admission, there was a little swelling about the eyes but none elsewhere On February 23, there was a slight general edema

During the period of study the temperature fluctuated somewhat from normal, rising to 100 F <sup>61</sup> or slightly above on a number of occasions

The systolic blood pressure varied between 90 and 102 mm of mercury

During our study, cholesterol ranged from 420 to 500 mg, and nonprotein nitrogen from 29 to 31.5 mg per hundred cubic centimeters of blood, with one questionable determination of 48 mg

On February 21, a low protein diet was given, on February 22, a low protein, salt-poor diet, on February 23, a carbohydrate diet, with no milk, and on February 26, a low protein, salt-poor diet. Water was not restricted.

On February 26, bismuth subcarbonate was administered, it was discontinued on March 3.

CASE 3-II—The same child as in case 3-I was admitted to the hospital for the fourth time on Nov 4, 1930. From 1929 until that time there had been several mild attacks of edema at home. Ten days before admission the child had had a cold and sore throat, and a few days later some swelling had appeared about the eyes followed by swelling of the feet and ankles.

On admission there was slight puffiness under the eyes, pitting edema of the legs and albumin 3 plus, but no red blood cells in the urine. In the hospital the temperature fluctuated above and below 99 F,<sup>61</sup> occasionally rising to 100 F, or slightly above, until January 24, when it was above 102 F on two examinations. It dropped somewhat during the next two days but fluctuated from about 100 to 101.5 F until January 30, when it subsided, and it reached normal on January 31. During this study, cholesterol varied from 420 to 610 mg, and nonprotein nitrogen from 28.5 to 39 mg, per hundred cubic centimeters of blood.

On November 4, a general diet was given, on November 6, a low protein, salt-poor diet, on November 10, a general diet, salt-poor, plus high vitamin content, on December 1, a general diet with high vitamin content, on December 5, a salt-poor, low protein, high vitamin diet, on Jan 3, 1931, a general diet, with high vitamin content, on January 6, a high protein, high vitamin diet, and on January 9, a high protein, salt-poor, high vitamin diet. Water was not restricted.

On December 5, magnesium sulphate was administered, it was discontinued on December 6.

#### CASE 4—*Glomerular Nephritis with Nephrotic Syndrome*

A girl, aged 10 years and 7 months, was admitted to the hospital on May 20, 1931. She had become ill about three months before with pain in the calves of the legs followed within one day by swelling of the feet, legs and ankles. The swelling rapidly increased, involving the thighs, abdomen and face. When she was kept in bed, the legs became less swollen but the buttocks and back more swollen. The swelling of the face and abdomen fluctuated from time to time. From the beginning of the illness the quantity of urine had been small, about a "cupful" a day, and the color yellow, not bloody or dark. For about a year the child had had severe frontal and occipital headaches lasting a day, with, at times, spots and queer lights before the eyes, usually associated with the headaches.

On admission the child did not seem acutely ill, the face was puffy, there was some edema of the neck, back, abdomen and buttocks, with marked edema of the thighs and legs. The heart was normal, and the systolic blood pressure was 84 mm of mercury. The systolic pressure was 98 on May 28, 98 on June 2, 142 on June 8, 140 on June 11 and 132 on June 13, after that date it varied between 114 and 138, until July 18, when it was 120. From July 27 to September 31, the range was from 104 to 124 mm of mercury. During our study, cholesterol varied from 420 to 635 mg, and nonprotein nitrogen from 28.5 to 32.5 mg, per hundred cubic centimeters of blood. The temperature was within normal range, except that it reached 100 F<sup>61</sup> or a little above on several occasions and that there was a period of fever on June 12, 13 and 14, with the temperature as high as 102 F or a little above each day. During this period of fever the pharynx was very red, the tonsils were hyperemic and swollen, and there was some pain in the throat.

On May 21, a low protein, salt-poor diet<sup>62</sup> was given, on May 22, a high protein, high vitamin diet, after June 19, a high protein, high vitamin, salt-poor diet. Water was not restricted.

Cascara was occasionally given as a laxative. On June 13, a few doses of acetylsalicylic acid were given for pain and fever.

#### CASE 5—*Acute Glomerular Nephritis with Nephrotic Syndrome*

A girl, aged 8 years, was admitted to the hospital on Dec 16, 1928, for an illness which began one week before with sore throat and "cold," with cough and vomiting. Puffiness of the face was noted, and there was pain in the knees about three or four days before admission. The abdomen had been swollen, and there had been headache, which was less at the time of admission. There was no drowsiness. The urine had been reduced in amount, and a physician found a great deal of albumin.

On admission, there was slight edema of the scalp, moderate edema of both legs and ascites. The urine showed albumin 3 plus with no red blood cells, and the benzidine test was negative. During the period included in our study, the systolic blood pressure varied between 88 and 92 mm of mercury, and the temperature was below 100 F,<sup>61</sup> except that it was approximately 100.8 F on one examination on December 17, and again on December 19. A few red blood cells were found in the urine several weeks after admission. The albumin was rather small in amount, with low specific gravity, and there was good excretion of water. During our study, cholesterol was 450, 450, 470, 400 and 330 mg, and nonprotein nitrogen from 24 to 36.5 mg per hundred cubic centimeters of blood.

On Dec 16, 1928, a low protein, salt-poor diet<sup>62</sup> was given, on December 17, a general diet, on Jan 23, 1929, a general diet, salt-poor, and on February 15, a general diet. Water was not restricted.

No drugs were administered that have any bearing on the study.

#### CASE 6—*Chronic Glomerular Nephritis with Nephrotic Syndrome*

A boy, aged 12 years and 4 months, was admitted to the hospital on Oct 2, 1928. He had been well until two weeks previously, when swelling of the face, especially about the eyes, appeared. This improved during the week before admission. It had come and gone, having last disappeared on September 30 and having returned in a slight degree on October 1. On admission, there was no edema of the face or of the scrotum.

The blood pressure was 120 systolic and 90 diastolic on October 4, and 110 systolic and 80 diastolic on October 30. In our study cholesterol varied from 370 to 420 mg, and nonprotein nitrogen from 31.5 to 39 mg, per hundred cubic centimeters of blood. The temperature was elevated from admission until October 9, rising to around 104 F<sup>61</sup> each day from October 3 to 8, inclusive. During this later period there was a diffuse bronchitis. After October 9 the temperature was practically within normal range.

On October 2, a general diet was given, which was continued during the child's entire stay in the hospital. Water was not restricted.

Acetylsalicylic acid was given occasionally.

#### CASE 7—*Acute Nephrosis (Acute Tubular Nephritis)*

A girl, aged 3 years and 3 months, was admitted to the hospital on Aug 26, 1928, as a patient of Dr George E. Baxter, who referred her to us for special study. One week before admission, the eyelids were seen to be swollen. The next day the abdomen was swollen, and the feet and legs subsequently became swollen. The child had had a slightly sore throat two weeks previous to the

present illness, and again at the time of the onset of the swelling. On admission, the eyelids were swollen sufficiently to close the eyes. There was marked edema of a general type, with the legs and thighs tense and glistening and with some edema of the upper extremities. There was a suggestion of movable dulness in the abdomen.

The urine on August 27 showed 3 plus albumin, but did not show red blood cells or casts. From September 11 to 15, albumin in the urine varied from 7 to 15 Gm per liter by Esbach's test. On September 17, the edema was nearly gone, with no puffiness of the face or swelling of the extremities and with albumin in the urine, 17 Gm per liter. During our study, cholesterol was 590, 580, 540 and 230 mg, and nonprotein nitrogen varied from 28 to 30.5 mg, per hundred cubic centimeters of blood. The systolic blood pressure on August 28 was 88 mm of mercury.

The temperature was within normal range during the entire period of study, except that it reached 100.2 F<sup>61</sup> on September 9, 100.4 on September 13 and 100 on September 16. The tonsils and adenoids were removed on September 13, and the child was discharged from the hospital on September 18.

On August 26, the diet consisted of milk not to exceed 1 pint (473 cc), other fluids not to exceed 1 pint, toast, cereals and other carbohydrates. On August 27, a salt-poor diet<sup>62</sup> was given with potatoes, vegetables and puddings without eggs permitted.

Beginning August 28, magnesium sulphate and magnesia magma were given irregularly.

Subsequent to leaving the hospital, the child was seen by Dr. Baxter on several occasions. On September 22, the albumin in the urine was 1 plus. There was no edema. In October there was more albumin, but on October 29 albumin was absent and the child had no edema. She had a cold in December and again in February, but on neither of these occasions was there any albuminuria. When seen by Dr. Baxter on March 5, 1929, the child was normal.

#### EXPLANATION OF CHARTS

The first chart for each case is intended especially to show the changes in the water content of the blood in relation to the changes in the course of the edema. Each column represents a specimen of blood with the proportion of the various constituents indicated by the height of the different markings explained in the key. The various elements are measurable in percentage of whole blood by the scale to the left.

The weight curve when considered in conjunction with the degree of pitting on pressure and the time (minutes) for disappearance of intradermally injected salt solution for the arm (*A*) and leg (*L*), given above on the chart, presents a picture of the degree and course of the edema.

Above, also, are given the results of examinations for protein and the number of red blood cells (per low power field in an uncentrifugated specimen) in single specimens of urine collected just after obtaining the specimen of blood.

The values for the red blood cell counts and the hemoglobin and hematocrit determinations are represented graphically below.

The values for viscosity and specific gravity of the whole blood, and for the percentage of water in the whole blood, plasma and cells, are given in figures at the bottom of the chart

The average values for our control cases and for normal cases from the literature are represented in the two columns to the right, and by the data below these columns

The normal values from the literature are based on the following data

**Total solids of whole blood** The average of six determinations from Lust<sup>63</sup> and three from Courtney and Fales<sup>64</sup> that fall within our range of ages was taken. This average is 18.95 per cent, which is very close to Brown and Rowntree's<sup>23b</sup> average of 19 per cent for normal adults

**Total solids of plasma** No data for children were found. Hawk and Bergeim<sup>46</sup> gave 8.2 per cent as normal. So, also, did Simon<sup>65</sup>. Brown and Rowntree<sup>23b</sup> gave 8 per cent as the average for fifty normal adults

**Cell solids** No data for children were found. Brown and Rowntree<sup>23b</sup> gave 36 per cent as the average for fifty normal adults

**Plasma protein, total and fractional** For normal children, the total serum proteins were reported as 7.3 per cent by Schwarz and Kohn<sup>36</sup> and as 7.6 per cent by Blackfan and Hamilton,<sup>37</sup> both values having been determined by Kjeldahl methods. However, for normal children we have found no values for plasma proteins, total or fractional, determined by either the Wu or the Howe method. Therefore, we used the following sources to arrive at our "normal values from the literature." By the Wu method, Wu,<sup>45</sup> using plasma, reported for "five normal bloods" averages of 6.94 per cent for total "serum protein," 4.85 per cent for albumin and 2.09 per cent for globulin. Fahr and Swanson<sup>31</sup> reported for nine normal adults averages of 7.2 per cent for total plasma protein, 4.9 per cent for albumin, 2.3 per cent for globulin including fibrinogen and 0.3 per cent for fibrinogen. By the Howe method, Linder, Lundsgaard and Van Slyke<sup>30</sup> reported for "seven normal plasmas" averages of 6.73 per cent for total protein, 4.11 per cent for albumin and 2.61 per cent for globulin including fibrinogen. Moore and Van Slyke<sup>32</sup> reported for heparinized blood of "nine normal subjects" averages of 7.1 per cent for total plasma protein, 4.3 per cent for albumin and 2.8 per cent for globulin including fibrinogen. By converting the foregoing figures into terms of total plasma protein, of plasma albumin and of plasma globulin not including fibrinogen, by use of the figure 0.3 per cent as normal for fibrinogen, and then taking the averages, we obtained the following: total plasma protein, 7.07 per cent, albumin, 4.54 per cent, globulin, 2.22 per cent, and fibrinogen, 0.3 per cent

**Specific gravity of blood** The average of Peiper's<sup>66</sup> figures for eleven normal children (eight boys and three girls) between the ages of 6 and 13 years was

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63 Lust, F. Die Viscositat des Blutes beim gesunden und kranken Saugling, Arch f Kinderh **54** 260, 1910

64 Courtney, A. M., and Fales, H. L. Variation in Infants of Total Blood Solids, and the Concentration of Sodium Chloride in Plasma, Am J Dis Child **14** 202, 1917

65 Simon, C. E. A Text Book of Physiological Chemistry, Philadelphia, Lea Brothers & Company, 1901

66 Peiper, E. Das spezifische Gewicht des menschlichen Blutes, Centralbl f klin Med **12** 217, 1891

taken This average is 1 0518, which falls within the range from 1 050 to 1 052 given by Simon<sup>65</sup> as normal for children Burton-Opitz<sup>67</sup> does not agree so well, giving 1 058 as normal for children between 2 and 4 years and 1 061 as normal after the sixth year

**Viscosity of blood** The average of six determinations from Lust<sup>63</sup> that fall in our range of ages is 3 965 The average of the figures that Hess<sup>53</sup> obtained for the age range from 1 to 10 years (male, 3 89, and female, 3 8), representing thirty-nine determinations, is 3 845 The final average for these two groups, 3 9, is the figure used

**Relative cell and plasma volumes** The figure used is an average of twenty-seven determinations for twenty-six normal children between the ages of 2 7 and 11 years, from Darrow, Soule and Buckman,<sup>68</sup> this average, 35 4 per cent for relative cell volume, corrected by 3 per cent (in accordance with the statement by two of these authors<sup>18</sup> as to the probable error in their hematocrit determinations due to hypertonicity of the ovalated specimens), is 36 5 per cent

**Hemoglobin** On each chart is recorded Williamson's<sup>69</sup> normal average for the age and sex of the patient in question

**Red blood cell count** Sahli<sup>70</sup> gave minimum and maximum figures from Perlman and Stoose (fourteen children of the ages of 3 years, and of from 11 to 14 years) that average 5,090,000 Sahli also gave four figures from Sorensen (children of from 2 to 10 years) that average 5,030,000 The final average for these two groups, 5,060,000, is used

The second chart for each case shows the changes in concentration of the plasma proteins in relation to changes in the course of the edema The albumin, fibrinogen and globulin fractions and the nonprotein solids of the plasma, if determined, are indicated on the columns by the various markings, which are interpreted in the key The values for these elements may be measured in percentage of plasma by the scale at the immediate left of the first column

The changes in the relative volume of plasma are indicated by curve *Pl* and may be read in percentages of whole blood by scale *Pl* to the left The state of the edema is indicated as in the first chart for each case, and the average values for the control cases and the normals from the literature are given in the two columns to the right

There are four charts for case 3, representing two attacks of edema

#### CASE 1—*Nephrosis*

Edema was first noticed about May 1 There had been no previous attacks of edema

67 Burton-Opitz, R A Text-Book of Physiology, Philadelphia, W B Saunders Company, 1920, p 163

68 Darrow, D C, Soule, H C, and Buckman, T E Blood Volume in Normal Infants and Children, J Clin Investigation 5 243, 1928

69 Williamson, C S Influence of Age and Sex on Hemoglobin, a Spectrophotometric Analysis of Nine Hundred and Nineteen Cases, Arch Int Med 18 505 (Oct) 1916

70 Sahli, H A Treatise on Diagnostic Methods of Examination, ed 2, edited by N B Potter, Philadelphia, W B Saunders Company 1920, p 763

In chart 1 *A*, the following points are illustrated On May 9, with edema increasing, the relative volume of the plasma was markedly below normal, two days later, with edema stationary, it was decidedly higher, and three days before the onset of diuresis it was further increased toward normal On May 23, with the edema gone, except for a slight pitting of the leg, the relative volume of the plasma had reached normal

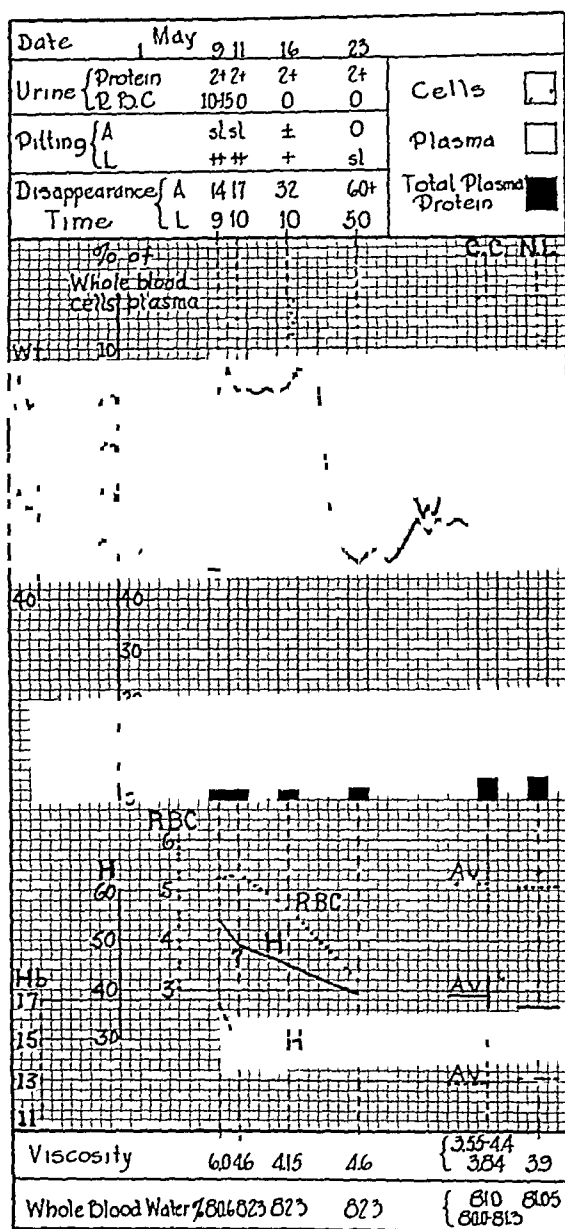


Chart 1 *A*—Data in case 1 The patient is a girl, aged 4 years and 7 months, with nephrosis The key to this and charts 1 *B* to 7 *B* follows *A* indicates arm, *L*, leg, *sl*, slight, *tr*, trace, *occ*, occasional, *lt*, little, *CC*, control cases, *NL*, normal cases from the literature, *W*, weight, *Hb*, hemoglobin, *H*, hematocrit reading, *RBC*, red blood cell count, or red blood cells, *Av*, average, and *Pl*, plasma The scale for hemoglobin in the *A* series of charts is in grams per hundred cubic centimeters of blood, for hematocrit, in per cent, and for red blood cell count, in millions



Here, then, we have a low relative volume of the plasma with edema increasing, which becomes relatively higher with edema stationary, before the onset of diuresis, and reaches normal with loss of edema

The viscosity of the blood was high during increasing edema, markedly lower with edema becoming stationary, still lower four days before the onset of diuresis, and somewhat higher again at the end of diuresis. It followed rather well the changes in the relative volume of the cells, except that on May 23, with the relative cell volume decreased, the viscosity was increased. At this time, however, the concentration of the total protein in the plasma was higher than at the previous determina-

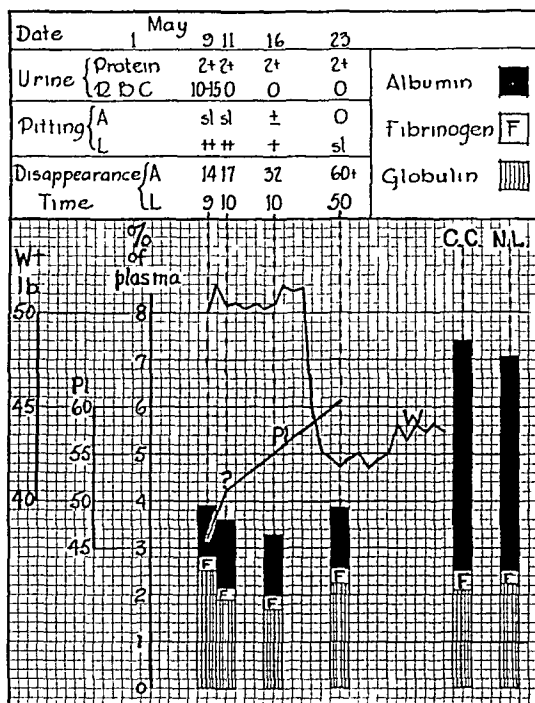


Chart 1 B—Data in case 1. The patient is a girl, aged 4 years and 7 months, with nephrosis. The scale for plasma (headed *PI*) in the B series of charts is in per cent of whole blood.

tion, and this may have contributed to the increase in viscosity. The time for the disappearance of intradermally injected salt solution for the arm was shortest with advancing edema, somewhat longer with edema stationary on May 11, and definitely longer on May 16 four days preceding diuresis, and normal at the end of diuresis. As is usual in edema, in our experience, the change toward normal of the disappearance time for the leg lagged behind that for the arm. We consider a change in the disappearance time for the arm a much better criterion of the course of the general edema than a change in the time for the leg.

In chart 1 B, it is seen that the concentration of the total protein of the plasma was low throughout with the concentration of the albumin

very low and that of the globulin nearly normal or somewhat higher than normal. There was no significant increase in the concentration of the protein in the plasma with diuresis.

If the values for the relative volume of plasma, represented in curve *PI* and measured in percentage of whole blood on the scale *PI* to the left, are compared with the values for total plasma protein and plasma albumin, it is seen that there is no direct relationship between changes

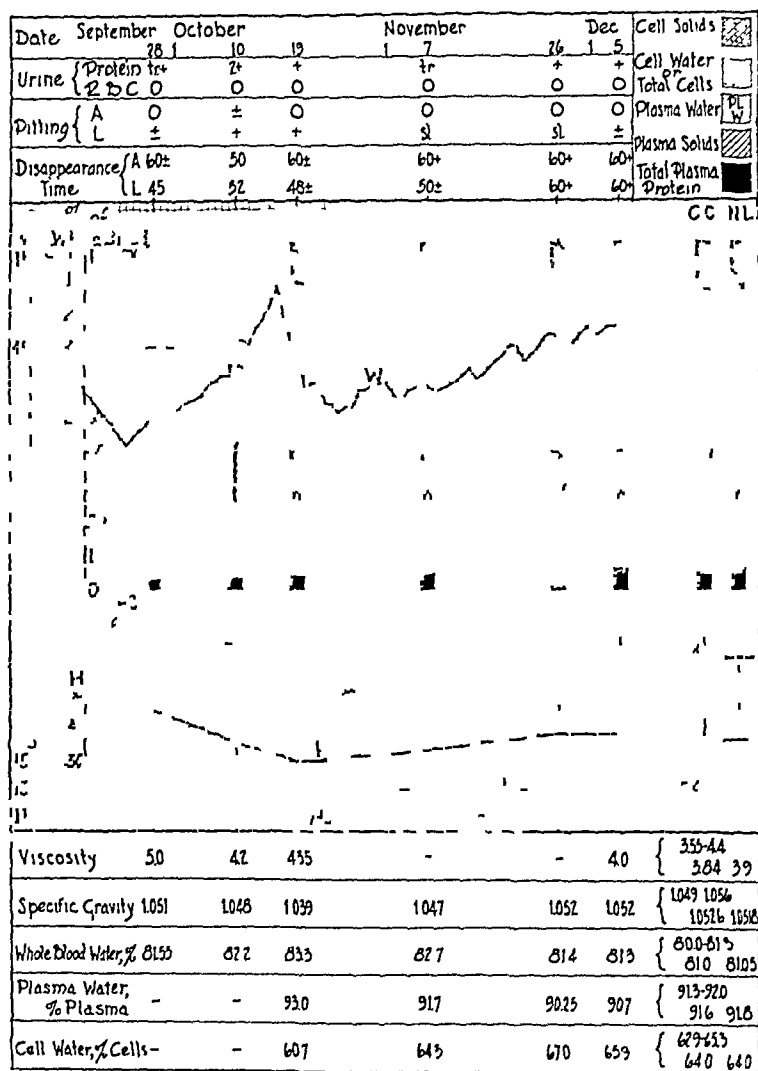


Chart 2 *A*—Data in case 2. The patient is a boy, aged 6 years and 12 months, with Hodgkin's disease and nephrosis.

in the relative volume of the plasma and changes in the concentration of the plasma proteins.

#### CASE 2—Hodgkin's Disease with Nephrosis

The patient was admitted to the hospital during his first attack of edema on September 13.

In chart 2 *A*, the following points are illustrated. On September 28, with the present attack of edema (the second one), just beginning, the

relative volume of the plasma was definitely low Eight days before the onset of diuresis, with the weight remaining unchanged on the next two days, the relative volume of the plasma was considerably higher, and was still higher having a value above normal during diuresis and the loss of edema The return of the relative volume of the plasma to normal during convalescence was slow

The increase of the relative volume of the plasma to a value so much above normal at the time of diuresis suggests a moderate anemia or a failure of normal excretion by the kidneys The latter possibility seems to gain support from the finding of high values for the nonprotein solids of the plasma on November 26 and December 5

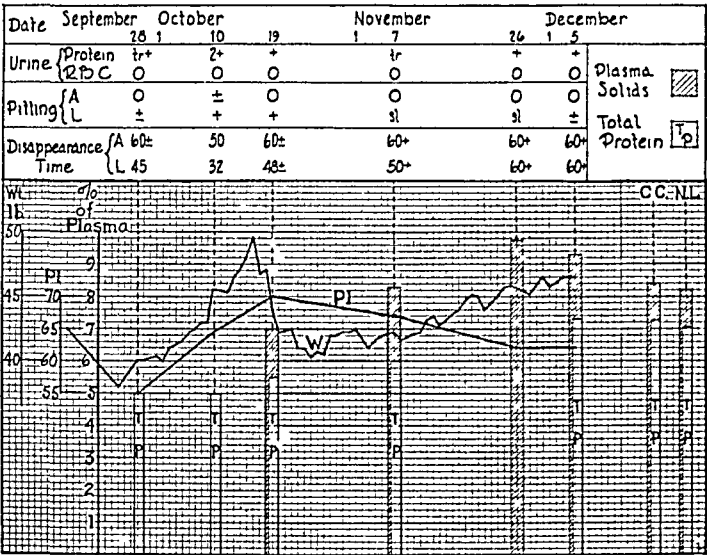


Chart 2 B—Data in case 2 The patient is a boy, aged 6 years and 9 months, with Hodgkin's disease and nephrosis

The viscosity of the whole blood, like the relative cell volume, was higher than normal with edema developing, and dropped preceding diuresis With diuresis, however, this relationship of the viscosity to the relative cell volume did not hold, possibly because of the increase in the protein concentration of the plasma

Chart 2 B shows that the concentration of total protein in the plasma was below the critical level for edema of Moore and Van Slyke <sup>71</sup> during

<sup>71</sup> Moore and Van Slyke <sup>32</sup> studied the relationship of the total protein and albumin content of the plasma to the presence or absence of edema in seventy-five cases of nephritis Edema was found in none of the patients with total plasma protein above the range of 55 Gm, plus or minus 0.3 Gm per hundred cubic centimeters, or albumin above the range of 2.5 Gm, plus or minus 0.2 Gm per hundred cubic centimeters (with one exception probably due to technical error), whereas edema was detectable by ordinary clinical observation in all with figures below these ranges

the period of development of edema, and within the range of the critical level on the fourth day of diuresis. The values for the non-protein solids of the plasma were high during the convalescent period.

CASE 3-I—*Chronic Glomerular Nephritis with Nephrotic Syndrome*

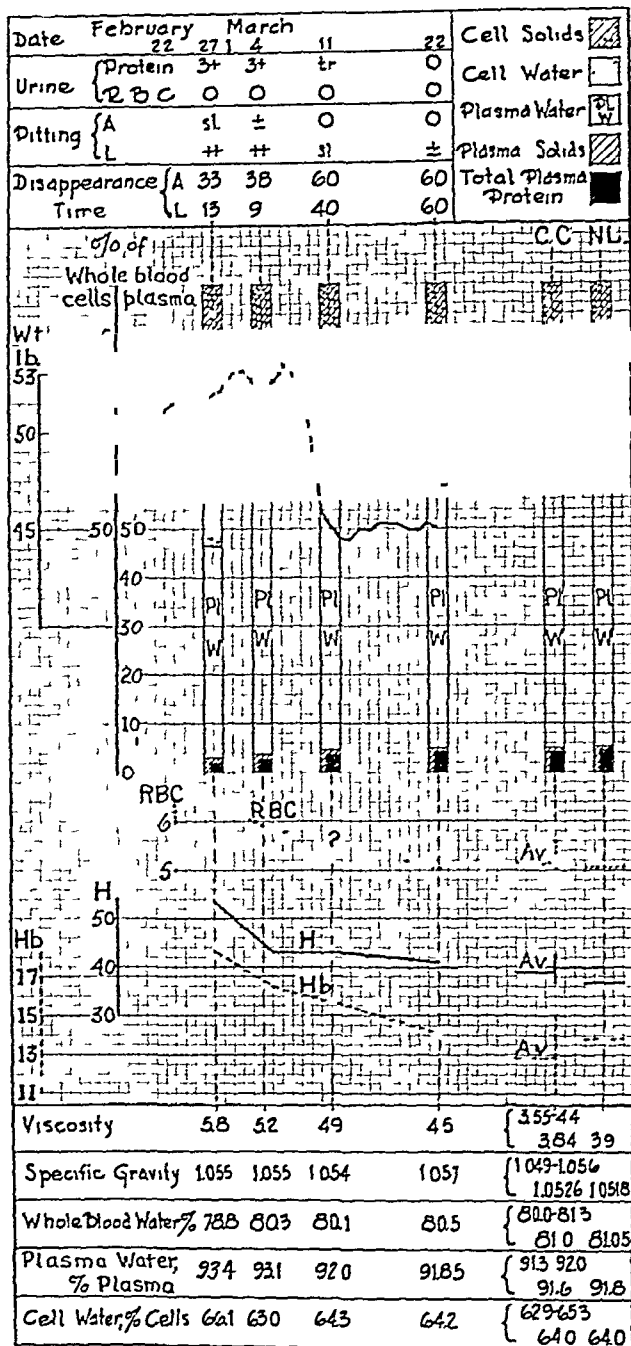


Chart 3-IA—Data in case 3, series I. The patient is a boy, aged 5 years and 4 months, having chronic glomerular nephritis with nephrotic syndrome.

This patient was studied during two periods of edema which were separated by an interval of about nineteen and a half months. There had been at least one previous attack of edema, in the fall of 1927.

In chart 3-I A, representing the first attack studied, a very low relative volume of plasma was present at the first test when the edema was

advancing This was markedly higher three days before the onset of diuresis and was practically normal ten days after the completion of diuresis

The viscosity of the blood was high during the development of the edema, somewhat lower before diuresis, and still lower just at the end of diuresis The changes in the relative volume of cells and viscosity were in the same direction The disappearance time of intradermally injected salt solution for the arm was longer on March 4 than on February 27

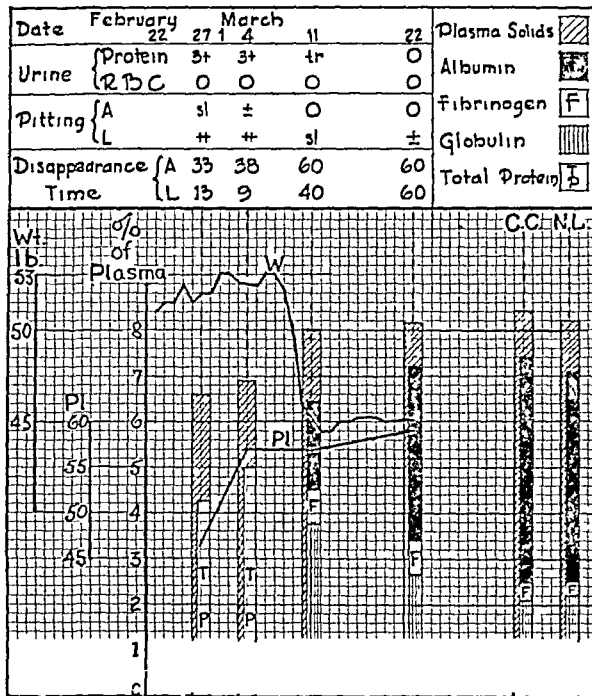


Chart 3-IB—Data in case 3, series I The patient is a boy, aged 5 years and 4 months, having chronic glomerular nephritis with nephrotic syndrome

Chart 3-IB shows that the concentration of the proteins of the plasma was low during the period of increase in the edema, a little higher during a stationary period three days before the onset of diuresis, and considerably higher at the end of diuresis, when, however, the albumin fraction was still below the critical level of Moore and Van Slyke for the presence of edema, although the total proteins of the plasma were above the critical level

A comparison of changes in the relative plasma volume, indicated by curve *Pl*, with changes in the concentration of total protein in the plasma shows fairly good agreement between the first and second determinations Subsequently, however, the total protein and albumin concentrations increased considerably with little change in the relative plasma

volume However, with the plasma proteins near the critical level for edema and with the relative plasma volume nearing normal in the second determination, a further increase of the relative plasma volume probably should not be expected with an increase in the concentration of total protein

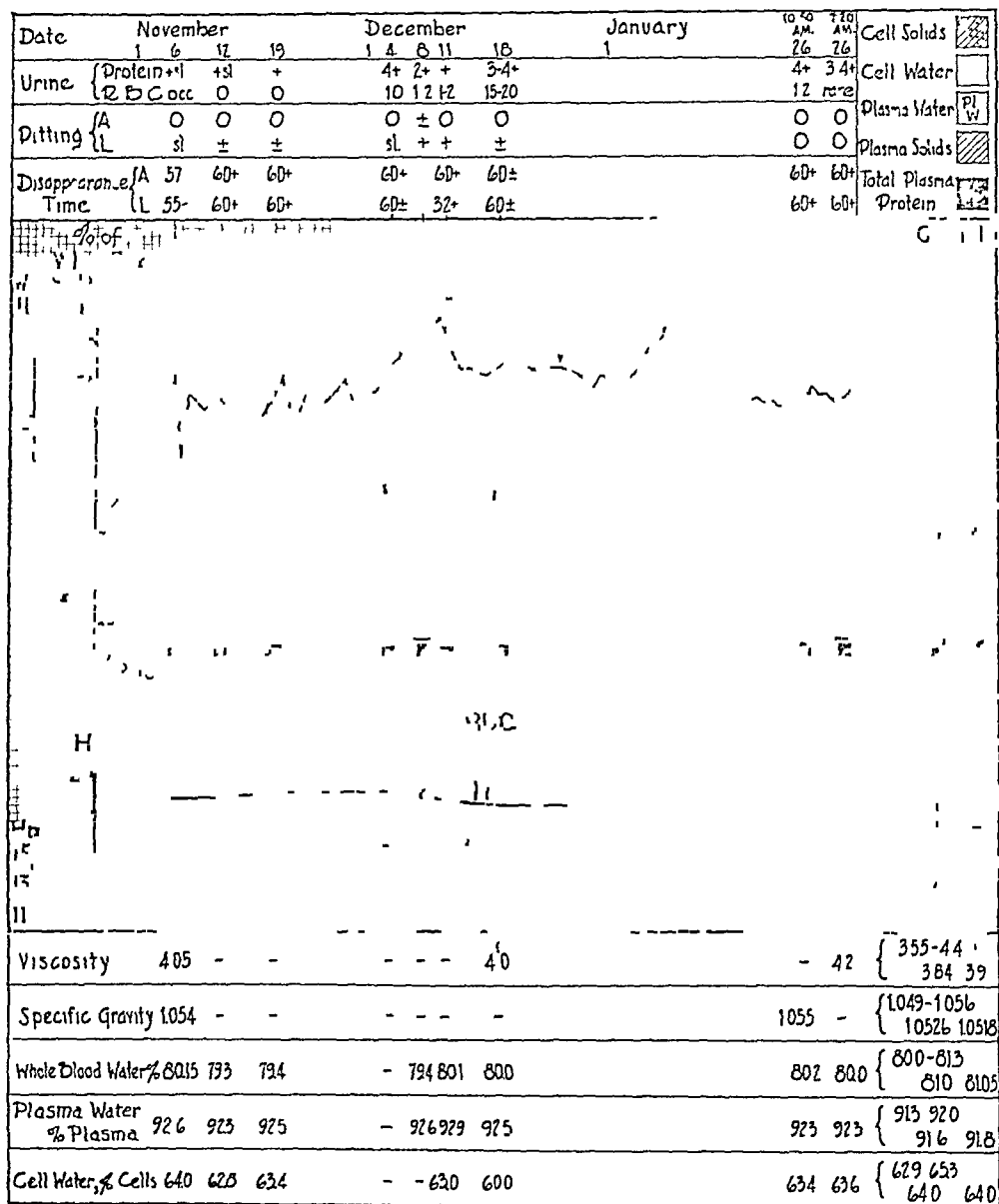


Chart 3-IIA—Data in case 3, series II The patient is the same boy as in case 3, series I, now aged 7 years, having chronic glomerular nephritis with nephrotic syndrome The hemoglobin determination of November 19 was made on an afternoon specimen of blood from the ear

CASE 3-II—The second series of determinations were begun during a period of subsiding edema and continued through a mild attack which appeared about a month later

Chart 3-II *A* shows that on December 4, during a period of advancing edema, the relative volume of the plasma is definitely less than the average for our controls and the average for normal children obtained from the literature. There was a slight increase in the relative volume on December 11 and 18, with the loss of weight and edema. There was no marked diuresis in this attack. The result of the determination on December 8 was discarded because of an accident in the manipulation.

Since the blood for our examinations was usually withdrawn about three hours after breakfast, it seemed desirable to see how this taking of food and fluids might influence the results of our tests. For this pur-

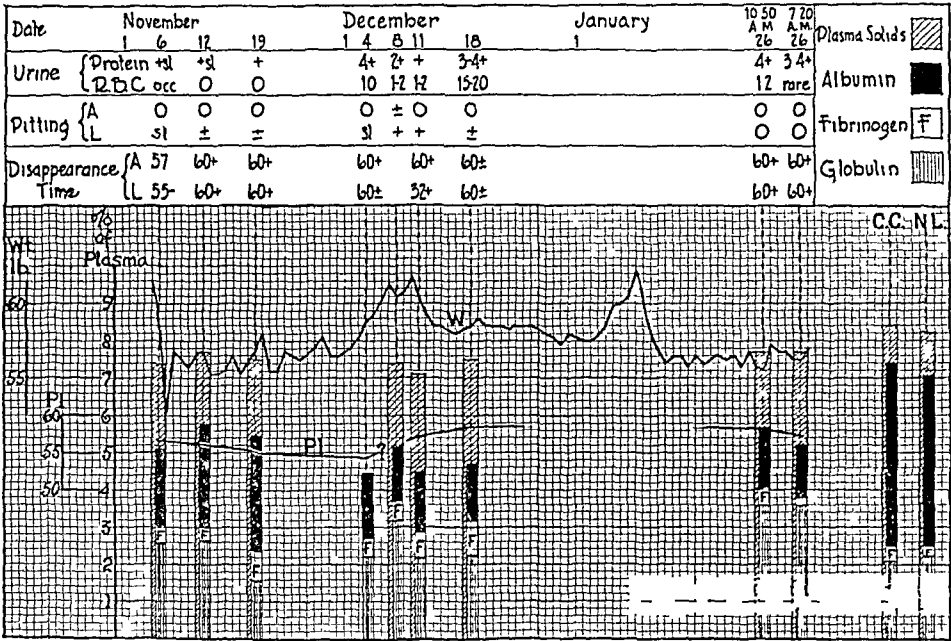


Chart 3-IIB—Data in case 3, series II. The patient is the same boy as in case 3, series I, now aged 7 years, having chronic glomerular nephritis with nephrotic syndrome.

pose on January 26, with edema absent, a specimen of blood was taken at 7 20 a m, when the patient had had no food or fluids since 8 p m on the previous day and another specimen at 10 50 a m, three and a quarter hours after breakfast. The results of these tests are shown in the two columns and appended data of January 26, the column to the left represents the data of the tests after breakfast. The decrease of 1 per cent in the relative volume of the plasma following breakfast is just within the limits of experimental error.

Chart 3-II *B* illustrates the following points. In the first three determinations, the total protein and the albumin of the plasma were just about at the critical level for edema. During the subsequent mild attack of edema the protein, especially the albumin fraction, was well

below the critical level. There was little change in the level of the albumin fraction throughout this attack of edema, it was lowest when the total protein was highest on December 8, two days before the weight curve began to fall.

The determinations of plasma protein before and after breakfast on January 26 seem to show a little increase in the albumin and fibrinogen fractions following the taking of food and fluids.

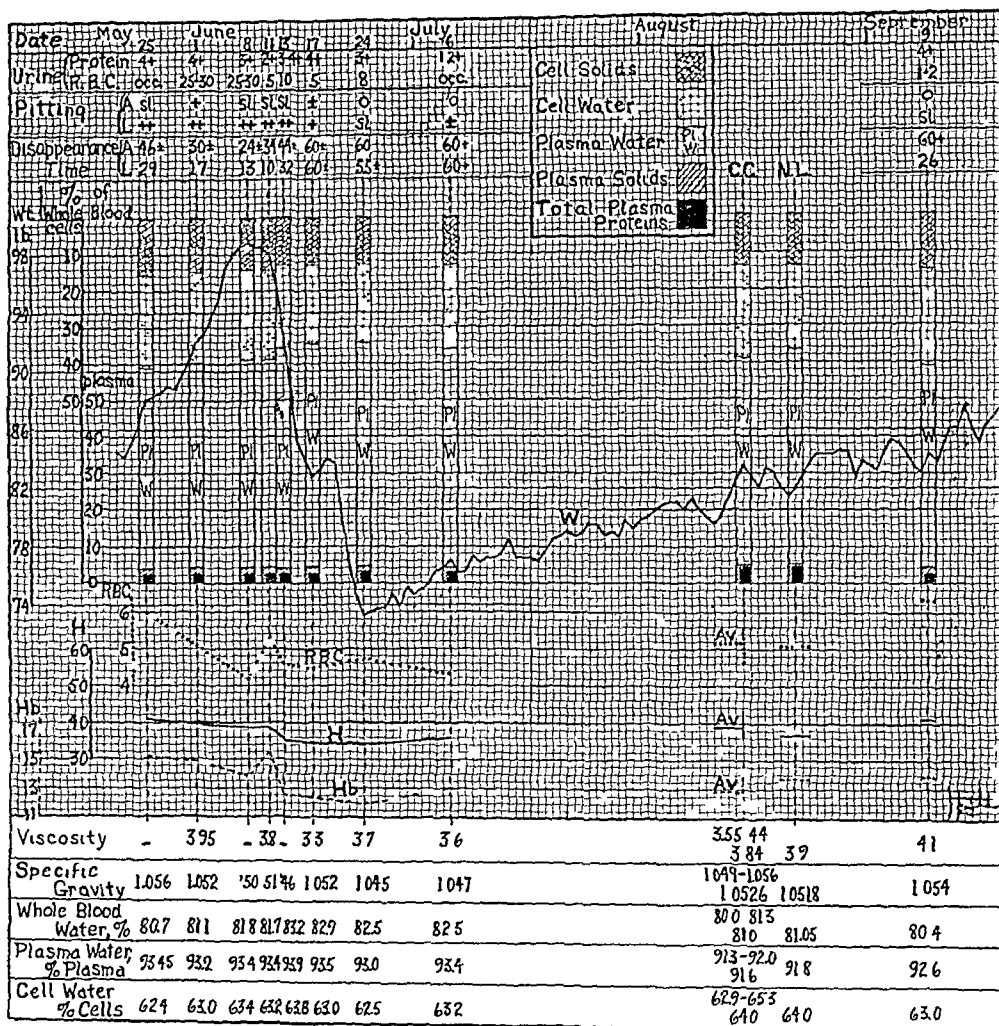


Chart 4A—Data in case 4. The patient is a girl, aged 10 years and 7 months, having glomerular nephritis with nephrotic syndrome.

The nonprotein solids of the plasma were high throughout, but were highest on December 11 and 18 when the edema was subsiding and when the plasma proteins were low.

#### CASE 4—Glomerular Nephritis with Nephrotic Syndrome

This attack of edema, the first one, began about three months before our first examination and fluctuated in degree from time to time.

Chart 4A shows that on May 25, with the edema increasing, the relative volume of the plasma was a little less than the normal average.



at the height of the weight curve, it was just about the normal, and during diuresis and loss of weight, it was a little above normal. On July 6, with the signs of edema gone except for questionable pitting of the leg, the relative volume of the plasma had returned toward normal. But, on September 9, with the disappearance time for the leg and a slight pitting of the leg suggesting a return of edema, the relative volume of the plasma was again a little less than the normal. The viscosity of the blood in a general way varied with changes in the relative cell volume, however, with a modification upward on June 24 when the concentration of the total proteins in the plasma was definitely increased. The disappearance time agreed quite well with the degree of the edema as indicated by pitting on pressure.

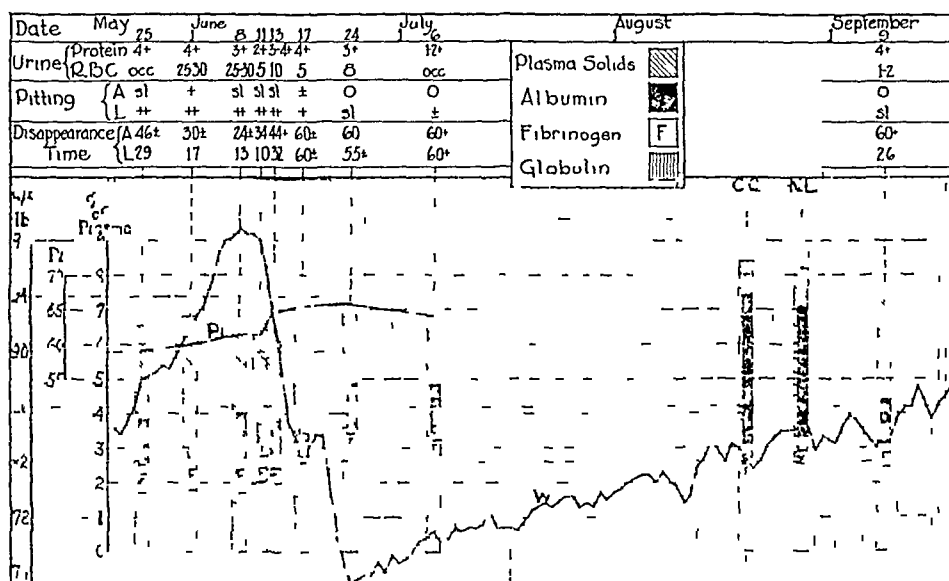


Chart 4B—Data in case 4. The patient is a girl, aged 10 years and 7 months, having glomerular nephritis with nephrotic syndrome.

Chart 4B shows that the total protein of the plasma and the albumin fraction were both markedly low during the advance of the edema. There was little change in the level of the total protein during diuresis and loss of weight, and the increase at the end of this period on June 24 was principally in the globulin fraction. On July 6, with only a slight or questionable pitting of the leg, together with a normal disappearance time, there was a slight increase in the albumin fraction with no further increase in total protein. This patient went through the entire cycle of edema from the time of our first determination with little change in the concentration of the total protein, and, especially, of the albumin fraction.

A comparison of the changes in curve *Pl*, representing relative plasma volume, with the changes in the total protein and albumin values

reveals no correlation. The nonprotein solids of the plasma were high with advancing and with subsiding edema, and were lowest on July 6 with edema practically gone.

### CASE 5—*Acute Glomerular Nephritis with Nephrotic Syndrome*

A first attack of edema with puffiness of the face was noted about four or five days before the first tests were made.

Date	December 17	January 2	9	16	20	Cell Solids
Urine {Protein	23+	1-2+	2+	0	0	Cell Water
{O.D.C.	0	0	0	0	0	Plasma Water
Pitting {A	sl	sl	0	0	0	Plasma Solids
{L	++	++	+	+	±	Total Plas
Disappearance {A	47±	34	60+	60+	60+	60+ Plasma Protein
{L	20	11	45±	47±		
Time						

Viscosity	40	37	355	355	36	355 44 384 39
Specif Gravity	1048	1047	1047	1046	1046	1049-1056 10526 10515
Whole Blood Water, %	819	827	820	819	8165	800-815 810 8105
Plasma Water, % Plasma	937	936	9285	926	922	915-920 916 918
Cell Water, % Cells	649	642	628	638	635	629-633 640 640

Chart 5A—Data in case 5. The patient is a girl, aged 8 years, having acute glomerular nephritis with nephrotic syndrome.

Chart 5A shows that the relative volume of the plasma was slightly below the normal average during the development of edema, and slightly above normal during diuresis. The viscosity of the whole blood was normal during the development and a little below normal during diuresis. The time for disappearance of intradermally injected salt solution agreed quite well with the degree of edema as shown by pitting on pressure.

Chart 5 *B* shows that on January 2, with diuresis well advanced, the total protein of the plasma was low. After this, it increased slowly. The nonprotein solids of the plasma were somewhat high, especially on January 16, when the edema was about gone. They were lower on January 30 with the plasma proteins approaching normal.

#### CASE 6—*Chronic Glomerular Nephritis with Nephrotic Syndrome*

A first attack of edema of rather slight degree, with swelling of the face, was noticed about September 18. The swelling increased and decreased intermittently and finally disappeared on September 30, but recurred on October 1.

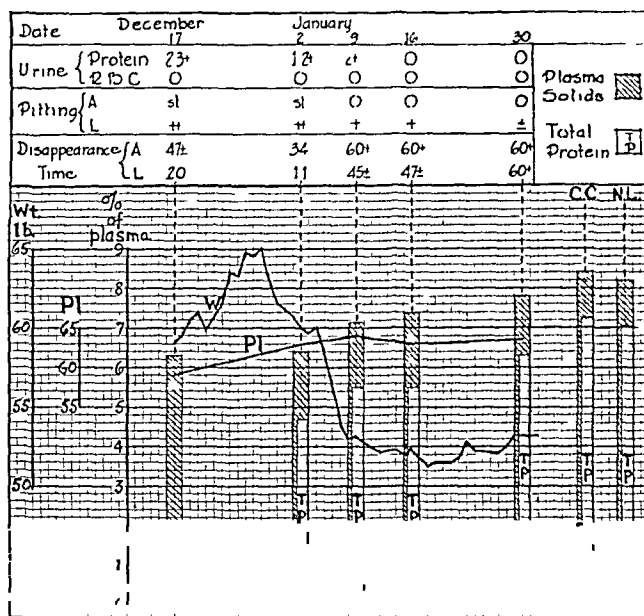


Chart 5B—Data in case 5. The patient is a girl, aged 8 years, having acute glomerular nephritis with nephrotic syndrome.

Chart 6 *A* shows that on October 5, with the edema still advancing, three days before diuresis, the relative volume of the plasma was less than the normal average. With loss of edema about complete on October 12, the relative volume of the plasma was about normal. The viscosity, slightly low on the first test, rose above normal with an increase of the relative cell volume, and was slightly higher on October 12 with a decrease of the relative cell volume. On the latter date, however, the concentration of the plasma protein was higher.

Chart 6 *B* shows that the total protein of the plasma was well below the critical level of Moore and Van Slyke<sup>71</sup> for edema when the diuresis was nearly complete, and that it was equally low three weeks later when no definite signs of edema could be made out. There was a high concentration of the nonprotein solids of the plasma during convales-



Chart 6A —Data in case 6 The patient is a boy, aged 12 years and 4 months, having chronic glomerular nephritis with nephrotic syndrome

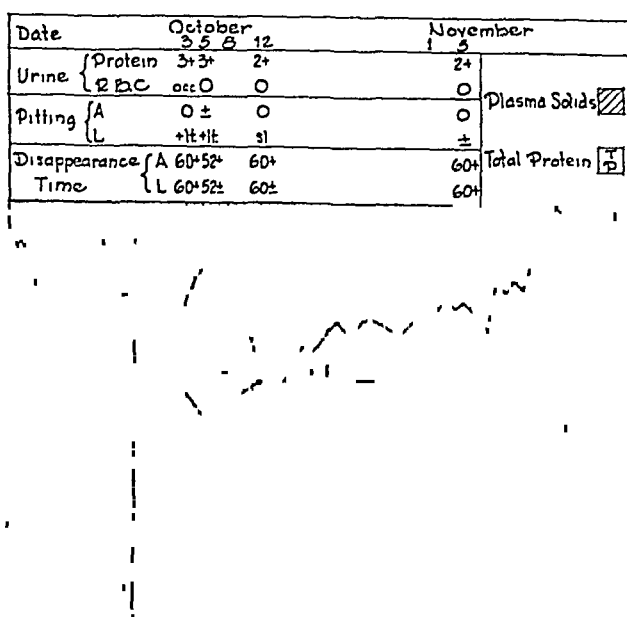


Chart 6B —Data in case 6 The patient is a boy, aged 12 years and 4 months having chronic glomerular nephritis with nephrotic syndrome

cence Changes in the relative volume of the plasma correlated fairly well with changes in the concentration of the total proteins in the few determinations made

### CASE 7—*Acute Nephrosis (Acute Tubular Nephritis)*

Date	September 5	17	November 14	
Urine { Protein	2+12±	12±	0	Cells <input type="checkbox"/>
{ E.P.C.	Occ	0	0	
{ A	± 0	0	0	Plasma <input type="checkbox"/>
{ L	+ 2	±	±	
Disappearance { A	50±48±	60±	60±	Total Plasma Protein <input checked="" type="checkbox"/>
Time { L	30±35±	60±	60±	
Wt	10.0			C.C. NL
Hb				
Ht				

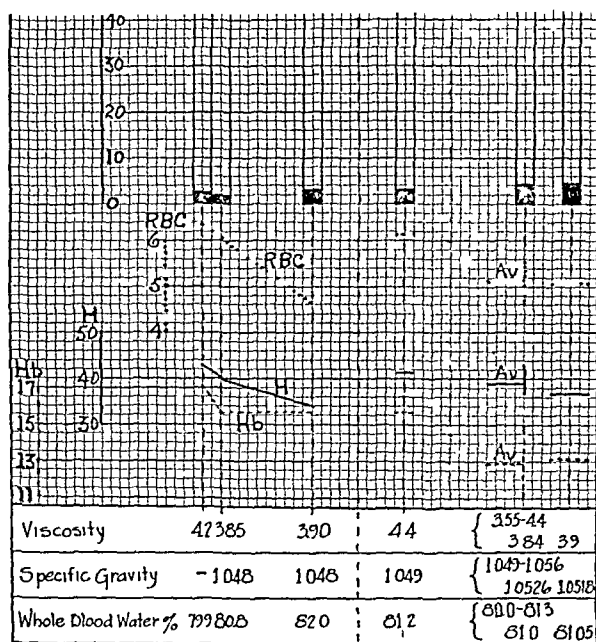


Chart 7A—Data in case 7 The patient is a girl, aged 3 years and 3 months, with acute nephrosis (acute tubular nephritis)

A first attack of edema of quite moderate grade, which began about August 19, was studied only during an irregularly subsiding phase

Chart 7A shows that on September 5, with the weight fluctuating, the relative volume of the plasma was a little less than the normal average. It was definitely greater than normal at the end of the decline in the edema and about normal two months later when the child was in

good condition. The viscosity and the relative cell volume, in general, changed in the same direction. The disappearance time corresponded rather well with the degree of edema as indicated by pitting.

Chart 7B shows that the values for the total protein of the plasma were low, with an abrupt decrease between September 5 and 7 which is unexplained. There was no evident relationship between the changes in the relative volume of the plasma, as indicated by curve *Pl*, and the changes in the concentration of total protein.

In chart 8 the columns show the relative volumes of plasma and cells in the different phases of edema. The solid black portion of each column represents plasma and the stippled portion represents cells. The

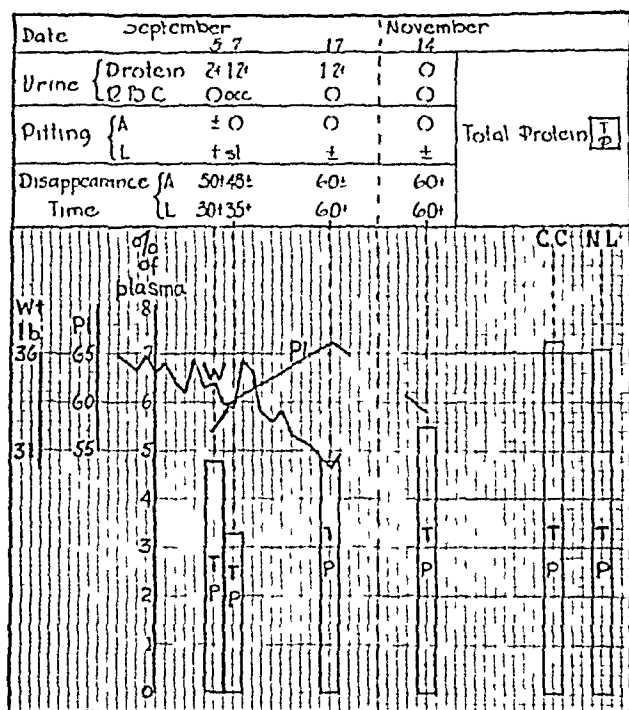


Chart 7B—Data in case 7 The patient is a girl, aged 3 years and 3 months, with acute nephrosis (acute tubular nephritis)

proportions of plasma and cells may be read in percentages of whole blood by means of the scale to the left. The cases are identified by the numbers at the bottom of the columns. Only cases that were studied in both the advancing and the subsiding phases of edema are included. The multiple width columns represent successive determinations in the same case on different days in the same phase of the edema. For case 3 two series of determinations, one for each of two attacks of edema, are indicated by columns 3-I and 3-II.

The heavy horizontal line crossing the middle of the chart marks the average relative volume of plasma for our controls, which is about 24 per cent lower than the average for normal children found in the literature.

It is seen that in every determination in the *developing phase* of edema, i e, at a time when edema was increasing, the relative volume of the plasma was below the average for the controls, in several instances it was markedly below

The *stationary phase* of edema is determined by the absence of active changes in the degree of edema as indicated by the weight curve, the figures for the fluid intake and the output of urine, the degree of pitting and the time for disappearance of intradermally injected salt solution considered together. In this phase, the relative volume of the plasma for each case was greater than it was in the previous phase and in one instance exceeded normal.

While the second determination in case 2 did not come at the highest point of the weight curve, yet it is placed in the phase of stationary

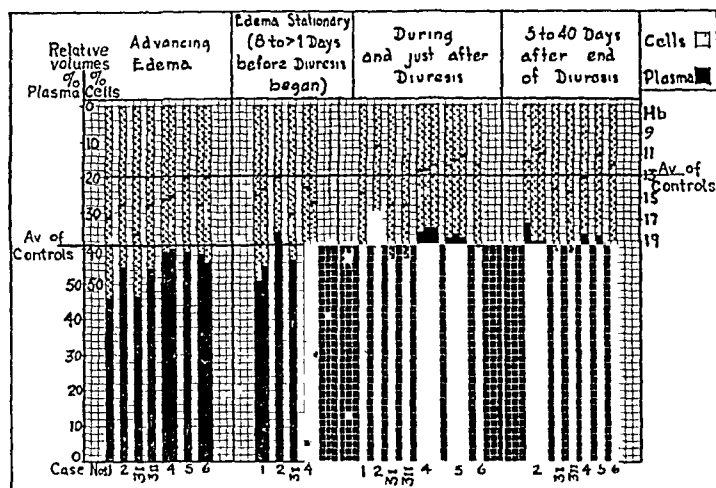


Chart 8—Relationship of relative plasma volume to phase of edema. The short horizontal lines represent hemoglobin value as measured in grams per hundred cubic centimeters of blood in scale, to right, headed *Hb*. *Av* indicates average.

edema, since the weight curve remained flat for the next two days following this test.

No determinations were made in the stationary phase in cases 5, 6 and 3-II. In the phase *during and just after diuresis*, the relative volume of the plasma was greater than in the previous phase in three cases, and unchanged in one case, while cases 5 and 3-II, with no determinations in the stationary phase, showed, however, a definitely greater relative volume of the plasma during diuresis than in the developing phase of edema. In two instances in the phase of diuresis and just after diuresis, the relative volume of the plasma was definitely higher than normal. Following diuresis the relative volumes of the plasma tended to attain an equilibrium close to the average normal.

For the purpose of showing to what degree movement of water from cells to plasma and the reverse might account for the variations in the relative volume of plasma, the value for hemoglobin, measurable in grams per hundred cubic centimeters of blood on the scale to the right, is indicated by the short, heavy horizontal line on the stippled portion of each column. The average of the hemoglobin determinations for the controls is indicated by the horizontal line at the level of 13 Gm per hundred cubic centimeters. It is seen that, in general, the hemoglobin value in the different phases of edema in the same case varies in a direction opposite to that of the changes in the relative volume of plasma and in the same direction as the changes in the relative cell volume, and that these changes in the hemoglobin are of about the same degree as the changes in the relative cell volume. This would not be so if shifting of water between cells and plasma accounted in considerable part for the changes in the relative cell volume, provided the absolute quantity of hemoglobin was not subjected to considerable change.

In chart 9, eighty-two determinations of the total protein and fifty-three of the albumin in the plasma in the various phases of edema of the renal type in twenty-three cases are presented to show the relationship between the concentration of the proteins in the plasma and the presence and the degree of edema. The symbols indicate the degree of edema, as determined by pitting of the arm and leg considered in conjunction with the time for disappearance of intradermally injected salt solution in the same regions at the time of the determination of the plasma proteins. In this classification, if pitting on pressure was questionable and the time for disappearance of intradermally injected salt solution was normal, edema was considered to be absent. The position of the symbol in relation to the scale to the left indicates the value for the total plasma protein, or the plasma albumin, in per cent of plasma. The heavy horizontal lines mark the limits of the critical levels of total protein and albumin in the plasma for the occurrence and nonoccurrence of edema, as determined by Moore and Van Slyke<sup>71</sup> for adults. The data charted to the right of the perpendicular line, both in the total protein and in the albumin group, are from the seven cases presented in detail in this paper. The data to the left of these lines represent determinations in sixteen other cases of the renal type of edema in children not presented in detail for reasons given under the discussion of the clinical material. If we take the open circles and squares as indicating the instances of definite edema, there is only one instance of definite edema in which the total protein of the plasma was above the upper limit of the critical level for edema of Moore and Van Slyke. If we consider edema to be absent in all instances represented by black circles and crosses, there are nine instances of absence of edema with the total protein of the plasma well



below the lower limit of the critical level. On analyzing the graph with respect to the albumin of the plasma similarly, there are no instances of definite edema with the albumin above the upper level of the critical level for edema. There are, however, six instances of absence of edema with the albumin of the plasma below the lower limit of the critical level. The greatest concentration of total protein, and of albumin, with edema present in our cases corresponds quite well with that found by Moore and Van Slyke for adults. The lowest concentration of total protein

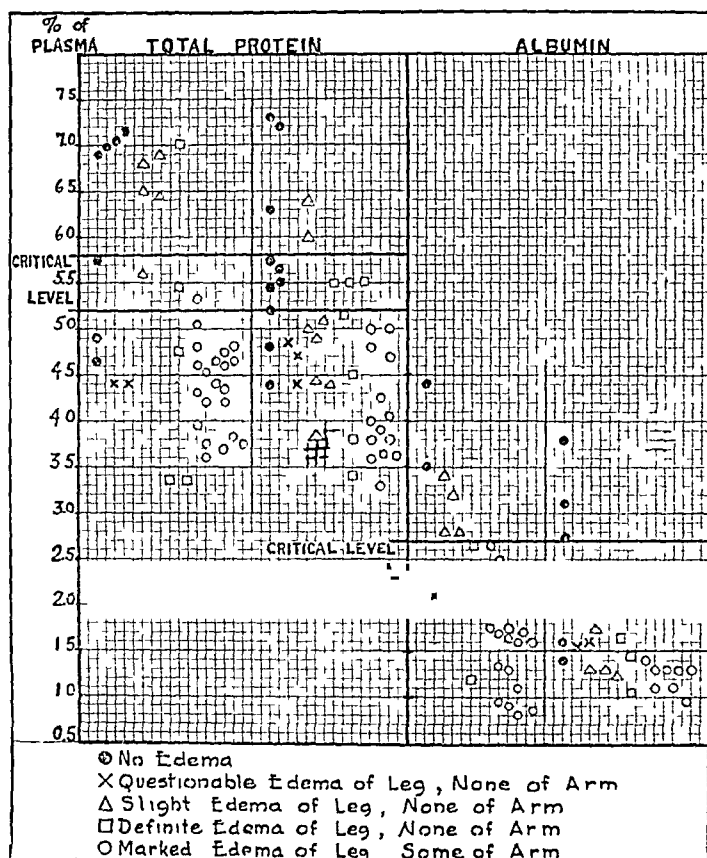


Chart 9—Concentration of plasma proteins in relation to edema

and of albumin in the absence of definite signs of edema in our cases, however, was in many instances well below that found by Moore and Van Slyke. These instances all occurred following subsidence of edema.

In our cases, with two exceptions subsequently noted, the concentration above which definite edema was always absent was 2.7 per cent for albumin, and 5.5 per cent for total protein of the plasma, and that below which definite edema was never absent was 1.2 per cent for albumin and 4.4 per cent for total protein. The exceptions to the foregoing rule were one instance in which there was 7 per cent total protein with

definite edema of the leg and none of the arm, and one instance in which there was 3.85 per cent total protein with only slight edema of the leg and none of the arm. The findings of Peters and associates<sup>13b</sup> concerning the lower limit of the concentration of serum proteins compatible with absence of edema are more in keeping with our results than are those of Moore and Van Slyke.<sup>71</sup>

In chart 10, the columns show the protein content of the plasma in the different phases of edema. The total height of the column represents the total protein content and the solid black portion the albumin content. In the instances in which the albumin is indicated in black, the stippled portion of the column represents the globulins including fibrin-

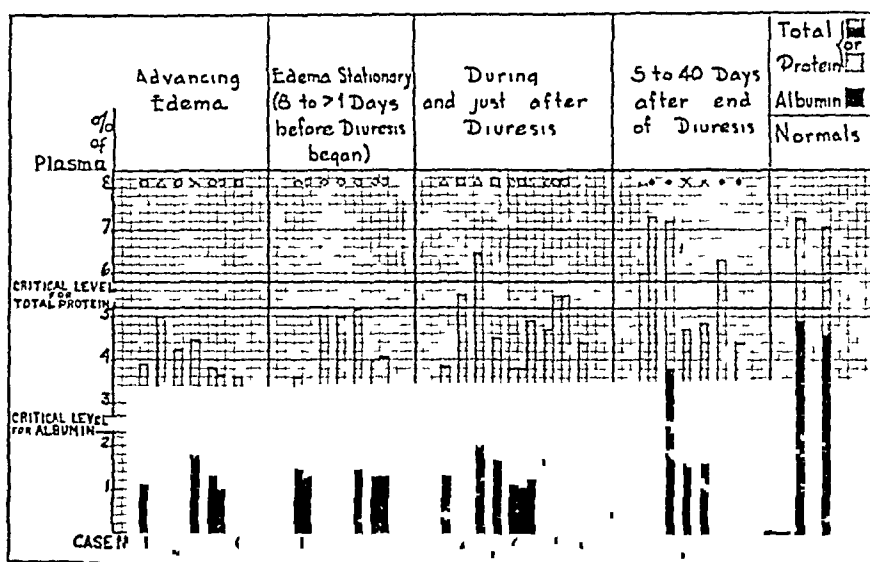


Chart 10—Relationship of plasma proteins to phase of edema. The symbols above the columns are explained in the key for chart 9. *CC* indicates control cases, and *NL*, normal cases from the literature.

ogen. The concentration of the protein constituents may be read in percentage of plasma by the scale to the left. The symbol above each column indicates the degree of edema as interpreted in the key for chart 9. The cases are the ones shown in chart 8 and are identified by the numbers below the columns as in that chart. The limits of the concentrations of total protein and albumin above which edema is usually absent and below which edema is usually present in adults, according to Moore and Van Slyke,<sup>71</sup> are indicated by the heavy horizontal lines crossing the chart. It is seen that during the advancing phase and during the stationary phase of edema preceding diuresis, the total protein and the albumin of the plasma were well below the critical level for edema in each instance. During the phase of diuresis and just after diuresis, the albumin fraction is still below the critical level in every instance (six determinations in four attacks of edema), and the total

protein is below the lower limit of the critical level for edema in seven of eleven determinations, in seven attacks of edema. Two of the instances in which the total protein is above the lower limit are in the same case. In other words, diuresis with subsidence of edema occurred when the plasma proteins, especially the albumin, were still in the range in which they are accredited with causing edema. From five to forty days after diuresis, with definite edema absent, the albumin in two of three determinations and the total protein in three of seven determinations are still very low. These data suggest that the increase in albumin and total protein of the plasma follows or accompanies rather than initiates diuresis with loss of edema.

Considering the data more generally, a material change in the relative volume of the cells during the cycle of the edema was accompanied by changes in the same direction of the red blood cell count, of the concentration of total blood solids and of hemoglobin, with some sporadic exceptions in these several elements, and when the relative volume of the cells showed little or no change from the preceding determination there was usually little or no change in these other elements.

The specific gravity of the blood in some cases tended to follow the relative volume of the cells, but in other cases it was little affected by changes in the latter.

The viscosity of the whole blood also tended to increase and decrease with similar changes in the relative volume of the cells. This relationship, however, seemed to be definitely modified in some instances by changes in the concentration of the plasma protein in that an increase or decrease in the protein tended to be accompanied by a corresponding modification in the viscosity.

In evaluating changes in the concentration of the whole blood solids it must be kept in mind that normally the concentration of solids in the cells is about four times that in the plasma and that, therefore, a decrease of the relative volume of the plasma will cause an increase in the percentage of the solids in the whole blood, provided that a coincident decrease in the concentration of the solids in the plasma sufficient to counterbalance this does not occur. We found that, like the relative cell volume, the total solids of the blood were in general highest during the development of edema, in some cases higher than normal notwithstanding a dilute plasma, and lowest just before or during diuresis. The concentration of the solids in the plasma, except for three determinations in case 2, was low throughout the course of edema because of the low content of albumin in the plasma. The fibrinogen and other globulins were frequently above normal. The nonprotein solids of the plasma were usually high, in some cases highest during edema and lower during diuresis and later, and in other cases highest after diuresis.

The cholesterol content of the blood, as a rule markedly high during edema, changed little during diuresis and was slow in returning toward normal following diuresis and subsidence of edema

The time for disappearance of intradermally injected salt solution in the arm and leg corresponded quite well to the degree of edema as determined by pitting on pressure in the same regions. In cases 1 and 3-I, while the weight curve remained level an increase in the disappearance time in the arm occurred several days before the onset of diuresis, thus forecasting an improvement. The change in degree of pitting on pressure also indicated a decrease of edema in the arm at this time. In case 4, also, the disappearance time in the arm was increased on the morning preceding the onset of definite diuresis and loss in weight.

The nonprotein nitrogen content of the blood was above 35 mg per hundred cubic centimeters in only four instances, 36.3 mg in one case, 39.2 mg, and 38.4 mg in another case, and 48 mg in a questionable determination in a third case. In the last case, however, the nonprotein nitrogen was 30 mg five days later and remained normal thereafter. In no instance was the nonprotein nitrogen found above normal in a case of nephrosis.

The protein content of the urine (estimated approximately in single specimens) did not as a rule show a definite decrease in the stage just preceding diuresis, as compared with the stage of developing edema.

#### COMMENT

In a composite case based on the data from the seven cases, the typical findings in the different phases of the edema cycle would be approximately as follows:

I In the developing phase a relative volume of plasma of less than normal, a plasma more dilute than normal because of a low concentration of albumin, but with a concentration of fibrinogen and globulin normal or slightly higher than normal, and with nonprotein solids above normal.

II With edema becoming stationary, preceding onset of diuresis, as compared with the phase of actively developing edema a greater relative volume of plasma, with the concentration of albumin, globulin and fibrinogen about the same, less edema of the arm, as indicated by less pitting on pressure, and a longer time for disappearance of intradermally injected salt solution.

III During diuresis, or just at its end, as compared with the stationary phase of edema a relative volume of plasma further increased and tending to be greater than normal, a concentration of albumin still at about the same low level, and a concentration of globulin somewhat above normal, a rapid subsidence of edema.

IV In the phase following diuresis a gradual return of the composition of the blood toward normal

The first increase of plasma proteins is more evident in the globulin fraction and may occur either in the third or in the fourth phase. The globulin later recedes toward normal as the albumin fraction advances toward normal.

We consider that a substantial decrease of the relative volume of the plasma in our cases indicates a movement of fluids from the blood to the tissues, and, conversely, a substantial increase of the relative volume of the plasma a movement of fluids from the tissues to the blood. The correctness of this interpretation depends on the presence of a relatively constant absolute volume of blood cells. In our cases, there is no reason to suspect that there was an abnormally rapid production of erythrocytes during the phase of actively developing edema, followed by a rapid loss of erythrocytes shortly before and during diuresis, as would be necessary to produce, by this means, the low relative volume of plasma found in actively developing edema, with the subsequent increase of the relative volume of plasma shortly before and during diuresis. The determinations of the relative volume of plasma in most cases were made at such short intervals during the critical stages in the edema cycle that gradual changes in the absolute volume of cells, such as might result from slowly progressing anemia, would not seem significant in this relation. From these considerations, therefore, we believe that we are justified in assuming that a substantial change in the relative volume of the plasma indicates an actual change in the absolute volume of the plasma and hence in the water content of the blood.

Against the possibility that the changes in the relative volumes of cells and plasma were due to shifting of water between the plasma and the cells, we found that the changes in the cell water (when the data were adequate for this calculation) were sufficient to account for only some of the small changes and small portions of the larger changes, found in the relative volume of the plasma.

The findings of some of the investigators of the blood and plasma volumes and of the protein concentrations in the plasma during the cycle of edema of the renal type are reviewed in the first portion of this paper. To summarize briefly. Although the studies of Bock<sup>22</sup> and of Brown and Rowntree<sup>23</sup> by a dye method would seem to show no changes in the volume of the plasma attributable to changes in the course of the edema, on the other hand observations on the red blood cell count by Keller<sup>9</sup> and by Nonnenbruch<sup>10</sup> furnish evidence tending to indicate the presence of a low volume of the plasma in the advancing stage of renal edema, as is indicated also by our findings. By methods for the determination of blood and plasma volume, Linder, Lundsgaard, Van Slyke and Stillman,<sup>17</sup> Plesch,<sup>20</sup> Darlow and Buckman<sup>18</sup> and Waterfield<sup>21</sup> also found

that the volume of the plasma is low during edema and increases with subsidence of edema in certain cases of the renal type

There is much evidence in the literature that the concentration of protein in the plasma is low in the active stage of renal edema, especially that of the nephrotic type. That it may be low also in some cases during and after subsidence of edema of renal type is shown by the findings of Fahr and Swanson,<sup>31</sup> Moore and Van Slyke,<sup>32</sup> Schwarz and Kohn,<sup>36</sup> Van Slyke and co-workers,<sup>5</sup> Linder, Lundsgaard and Van Slyke<sup>30</sup> and Calvin and Goldberg<sup>38</sup>. Also, Cowie and co-workers<sup>72</sup> reported that in a child with chronic glomerular nephritis in the nephrotic subgroup the serum contained 3.8 per cent total protein and 1.3 per cent albumin during an edema-free period. For the presence of a relative and at times an absolute increase of the globulin and fibrinogen fractions of the plasma protein in this type of edema, there is also considerable support in the literature.

From a consideration of our findings and of the data from the literature, it seems probable that during the actively developing stage of edema of nephrotic type an imbalance exists in the exchange of water between the blood and the tissues that results in a net loss of water by the blood and thus renders water relatively unavailable for excretion by the kidneys. This could be due to (a) a change in the tissues of the body in general that renders water less freely available for resorption by the blood, or (b) a change in the blood that decreases its power to resorb water from the tissues, or (c) both *a* and *b*. Later, preceding diuresis, the tissues lose some of their excessive water to the blood, and when the water in the blood reaches a sufficiently high level, diuresis begins and is continued by further flow of water from the tissues to the blood, with a consequent disappearance of the edema. The factor that is responsible for the movement of the excessive water from the tissues to the blood could be (a) a change toward normal in the tissues that renders the water more freely available for resorption by the blood, or (b) a change toward normal in the blood that increases its power to resorb water from the tissues, or (c) both *a* and *b*.

Starling<sup>24</sup> accredited the effect of the proteins on the osmotic pressure of the blood plasma with the function of maintaining a balance in the exchange of fluids between the tissues and the blood under normal conditions. On the basis of Starling's theory, Epstein has attributed edema of the nephrotic type to the low concentration of proteins in the plasma in that condition. The lack of a definite increase, and the occasional occurrence of a decrease, in the concentration of the proteins in

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<sup>72</sup> Cowie, D. M., Jarvis, K. M., and Cooperstock, M., with technical assistance of Nakao, A. Metabolism Studies in Nephrosis with Special Reference to Relationship of Protein Intake to Nitrogen Retention, Edema and Albuminuria, *Am J Dis Child* **40** 465 (Sept.) 1930.

the plasma just preceding and during diuresis in the majority of our cases is against the theory that the low concentration of proteins in the plasma is the sole or the chief cause of the edema. Doubtless a low concentration of proteins in the plasma, with the resulting lowered osmotic pressure, favors the development of edema. However, if we are to consider that the low concentration of proteins is the sole cause of edema, we must look for some other factor which determined the onset of diuresis and subsidence of edema in our cases.

Against the probability that the low concentration of the plasma protein is responsible for the low relative volume of the plasma in the advancing stage of edema in our cases is the finding that the relative volume of the plasma usually increased without an increase, and at times even with a decrease, in the concentration of the proteins in the plasma. In this relation, we calculated by means of the factors, of Govaerts<sup>72</sup> the combined, theoretical osmotic pressure of the plasma albumin and globulins in the cases in which the protein fractions were determined, and found no correlation between changes in the protein osmotic pressure and changes in the relative volume of the plasma. At times, with an increase of the latter, the calculated osmotic pressure of the plasma proteins was found to be decreased. Theoretically, within the range of the influence of the concentration of the plasma protein on the formation or the subsidence of edema an increase in osmotic pressure should precede an increase in the relative volume of the plasma, and, therefore, at the new level of the relative volume of the plasma the osmotic pressure should be found to be greater than or at least equal to, its value at the previous level of the relative volume of the plasma.

Our observations are in accord with the findings of Kylin<sup>73</sup> and Meyer<sup>74</sup> that the colloidal osmotic pressure of the blood serum frequently remained low and at times even decreased during the disappearance of renal edema.

In evaluating changes in the concentrations of protein and albumin in the plasma from one determination to the next, probably the changes in the relative volume of the plasma should be taken into account, for, by themselves, the changes in the percentages of the plasma proteins do not reflect the changes in the absolute quantities of these proteins. The increases in the percentages of the protein which must be allowed for, in our cases, from a consideration of increases in plasma volumes would seem insignificant as regards a causal relationship of increased albumin in the plasma to initiation of diuresis (the allowance not exceed-

73 Kylin E. Studien über die Oedemausschwemmung, IV Über den kolloidosmotischen Druck des Blutserums während der Oedemausschwemmung, *Ztschr f d ges exper Med* **68** 746, 1929.

74 Meyer, P. Untersuchungen über den kolloidosmotischen Druck des Blutes I Oedem und Oedemausschwemmung, *Ztschr f klin Med* **115** 647, 1931.

ing 0.13 per cent in any instance), and of possible significance in only two cases as regards correlation of the values for total protein with the edema cycle, that is, in case 3-I a further increase of 0.96 per cent of total protein at a point just preceding diuresis, and in case 2 an increase of 0.86 per cent at a similar point in the cycle must be allowed for

#### SUMMARY

The water content of the whole blood and of the blood plasma and the protein content of the plasma were determined at intervals during the cycle of edema of the nephrotic type with the hope of obtaining information of value in disclosing the mechanism of the production of the edema. It was thought that such information might be useful particularly in indicating whether the failure of water elimination is directly attributable to disturbance of renal function, to changes in the tissues of the body in general or to a deficient concentration of proteins in the blood plasma. For example, one might expect to find (1) a high content of water in the blood during the development of edema becoming normal with diuresis and loss of edema, if the edema is primarily due to a failure of the water-excretory function of the kidneys, (2) a low or normal water content in the blood during the development of edema (unless there should be a concurrent edema of the blood) becoming higher preceding and during diuresis, if the edema is attributable to the holding back of water by the tissues of the body in general, and (3) the same changes as in (2), if the edema is due to a low concentration of proteins in the plasma, in this event, however, a decrease in the plasma proteins should theoretically precede the loss of water in the blood and an increase in the plasma proteins should precede the increase in the water of the blood and the onset of the evacuation of edema.

Seven cases of nephrosis and glomerular nephritis with the nephrotic syndrome in children were examined at intervals during the cycle of edema especially for changes in the relative volume of the plasma and in the concentration of the solids of the whole blood and of the plasma, and also for changes in the concentration of the proteins in the plasma. It seemed especially important to have determinations as early in the cycle of the edema as possible and again just before and just after the onset of diuresis.

Our findings, in general, were

- 1 The relative volume of the plasma was usually low during the development of edema, higher preceding diuresis, still higher and at times above normal during diuresis. It tended to return to normal following diuresis.



2 The concentration of albumin in the plasma was low during the development of edema with the globulins tending to be normal or slightly higher than normal. During diuresis the plasma proteins remained low with a little increase in some cases, usually most evident in the globulin fraction. After diuresis, in the cases in which the general condition of the patients showed definite improvement, the plasma protein gradually rose toward normal.

3 The concentration of nonprotein solids in the plasma was often greater than normal. This increase could not be accounted for by an increase in the nonprotein nitrogen elements and only partially by an increase in cholesterol content.<sup>75</sup>

We believe that changes in the water content of the blood in our cases are best reflected in the variations in the relative volume of the plasma.

The variations from normal of the relative volume of the plasma during the cycle of edema were just the reverse of what might have been expected if the edema was due entirely to a failure of the water-excretory function of the kidneys.

While the changes in the water content of the blood, considered alone, were, in general, consistent with the theory that low concentration of proteins in the plasma is the cause of edema, yet the fact that the onset of diuresis and loss of edema, in most instances, occurred without significant increase in the concentration of the plasma proteins, especially in that of the albumin fraction, indicates that some other factor, or factors, was important in maintaining the edema and probably, therefore, in producing it.

In the analysis of our data the amount of increase in the concentration of the proteins in the plasma preceding the onset of diuresis that may have been masked by a coincident increase in the volume of the plasma seems insignificant as regards any influence on the initiation of diuresis except possibly the increase in the total proteins of the plasma in the two instances previously discussed.

In considering the rôle of a low concentration of plasma protein in the production of edema, possibly one should differentiate between a favoring factor (one causing a tendency or susceptibility to the formation of edema) and an active factor (one determining the actual formation of a clinical edema) and consider the possibility that the withdrawal or abeyance of either of these factors might be sufficient to bring about loss of the edema. The low concentration of the plasma protein in edema

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<sup>75</sup> Kumpf, by a refractometric method, found the "non-protein constituents" of the serum high in certain cases of renal disease including one of nephrosis. Kumpf, A. E. *The Blood Proteins, with Special Reference to the Changes Occurring in Renal Diseases*, Arch. Path. **11** 336 (March) 1931.

of the nephrotic type may be such a favoring factor, and in its presence some additional, active factor may be necessary to bring about a manifest edema. On the other hand, the changes in the water content of the blood during the cycle of the edema are not inconsistent with what might be expected if the edema were due to changes in the tissues of the body in general rendering the water held by them less readily available for resorption by the blood during the development of edema, and freely available for resorption by the blood with improvement preceding and during diuresis.

The conception that the changes which lead to the subsidence of edema are primarily in the tissues gains support from the observation in two of our cases of a lengthening of the time for the disappearance of intradermally injected salt solution in the arm, without an increase in the calculated plasma osmotic pressure due to the proteins, during the stationary phase of edema preceding the onset of diuresis and loss of weight.

# CONGESTIVE HEART FAILURE AND ANGINA PECTORIS \*

THE THERAPEUTIC EFFECT OF THYROIDECTOMY ON PATIENTS  
WITHOUT CLINICAL OR PATHOLOGIC EVIDENCE OF  
THYROID TOXICITY

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Previous studies of the velocity of the blood flow in man<sup>1</sup> have shown that the adequacy of a given velocity of blood flow cannot be decided in absolute terms. It can be evaluated only in relation to the metabolic demands of the particular patient. The best gage of the metabolic needs of the tissues is the basal metabolic rate. Whether or not a patient with heart disease suffers from the signs and symptoms of circulatory insufficiency depends on whether the supply of blood is adequate to the metabolic demands of the tissues. In patients with congestive heart failure and a normal basal metabolic rate, the basal velocity of the blood flow is greatly slowed.<sup>2</sup> The blood flow

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\*Further studies in other types of cardiovascular disease are being made, and a more detailed account of precautions, indications and contraindications of the operation will be published in the near future. It is felt that until more experience is available, the operation should be confined to the types of cases described in this communication.

1 Blumgart, H. L., and Weiss, S. Studies on the Velocity of Blood Flow. II. The Velocity of Blood Flow in Normal Resting Individuals and a Critique of the Method Used, *J. Clin. Investigation* **4** 15, 1927, III. The Velocity of Blood Flow and Its Relation to Other Aspects of the Circulation in Patients with Rheumatic and Syphilitic Heart Disease, *ibid* **4** 149, 1927, IV. The Velocity of Blood Flow and Its Relation to Other Aspects of the Circulation in Patients with Arteriosclerosis and in Patients with Arterial Hypertension, *ibid* **4** 173, 1927. Blumgart, H. L., Gargill, S. L., and Gilligan, D. R. XIII. The Circulatory Response to Thyrotoxicosis, *ibid* **9** 69, 1930, XV. The Velocity of Blood Flow and Other Aspects of the Circulation in Patients with "Primary" and Secondary Anemia, *ibid*, **9** 679, 1931.

2 Blumgart, H. L., and Weiss, S. Clinical Studies on the Velocity of Blood Flow. IX. The Pulmonary Circulation Time, the Velocity of Venous Blood Flow to the Heart, and Related Aspects of the Circulation in Patients with Cardiovascular Disease, *J. Clin. Investigation* **5** 343, 1928, X. The Relation Between the Velocity of Blood Flow, the Venous Pressure and the Vital Capacity of the Lungs in Fifty Patients with Cardiovascular Disease Compared with Similar Measurements in Fifty Normal Persons, *ibid* **5** 379, 1928.

may be similarly slowed in patients with the low metabolic rate of myxedema,<sup>3</sup> but such patients show no clinical symptoms or signs of congestive heart failure. In these patients, therefore, the diminished circulation is evidently adequate to the diminished demands of the body.

The favorable effects of a reduction in the metabolic rate are seen in certain thyrotoxic patients with congestive failure whose circulation becomes compensated after subtotal thyroidectomy. The hearts of such patients are evidently equal to the demands of a normal metabolic rate, though not to the demands of the elevated metabolic rate of thyrotoxicosis. Because of these considerations, the possibility occurred to us that persons with normal metabolism who suffer from congestive heart failure might show striking improvement if the metabolic rate was significantly lowered. The hearts of such persons might be unable to supply enough blood for the ordinary demands of a normal metabolic rate, but might, nevertheless, be able to supply enough blood for the lessened needs of a reduced metabolic rate.

From the clinical standpoint, an observation made by one of us (S. A. L.)<sup>3a</sup> is of interest in the present problem. A patient who was suspected of having masked hyperthyroidism had a subtotal thyroidectomy performed in 1927. Examination of the gland showed a perfectly normal thyroid. In spite of that, however, the patient showed marked clinical improvement. This clinical observation was suggestive that the extirpation of the normal thyroid gland might be helpful in cardiac failure not due to thyrotoxicosis.

This communication presents the clinical results of producing a subnormal metabolic rate by thyroidectomy in three patients who were suffering from severe congestive heart failure but who showed no evidence of disturbed thyroid function and in one patient with angina pectoris with a slight elevation of metabolism but with a normal thyroid gland. The possible advantages of the procedure were offered to these patients because the signs and symptoms of circulatory insufficiency and of angina pectoris had persisted for a considerable time in spite of all known medical procedures. All subjects were completely incapacitated, and the possibility of improvement by all known methods of treatment seemed remote. These patients were chosen because the underlying cardiovascular condition was slowly progressive or relatively stationary, they showed no evidence of syphilitic heart disease, they were not too far advanced in years, and they showed no evidence

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3 Blumgart, H. L., Gargill, S. L., and Gilligan, D. R. Studies on the Velocity of Blood Flow. XIV. The Circulation in Myxedema with a Comparison of Blood Flow in Myxedema and Thyrotoxicosis, *J. Clin. Investigation* **9** 91, 1930.

3a Rosenblum, H. H., and Levine, S. A. What Happens to Patients with Hyperthyroidism and Significant Heart Disease Following Subtotal Thyroidectomy? *Am. J. M. Sc.* **185** 219, 1933.

of active infection. The patients were not gravely ill and the operative risk appeared to be fair. The clinical condition of each patient was accurately studied during a long control period in order that any change following thyroidectomy could be attributed confidently to the effect of the procedure.

#### REPORT OF CASES

CASE 1—I B, a man, aged 45, entered Beth Israel Hospital on Sept 13, 1932, complaining of shortness of breath of two and a half years' duration. His past history was irrelevant, except for recurrent cholecystitis during the previous twenty years. There was no history of rheumatic infection, diphtheria or venereal disease. During the preceding five years he had had nocturia three or four times. Two and a half years before admission he first noticed shortness of breath and fatigue on walking up hills or on walking up one or two flights of stairs. Soon after the onset of these symptoms, while waiting for a street-car one day, he was suddenly seized with a "tearing, breaking" pain over the entire front of his chest, not related to respiration. The pain lasted ten minutes, and then disappeared as suddenly as it had appeared.

Two years before admission the patient was troubled with dyspnea and palpitation even when he walked on a level surface. On admission to the hospital at that time he had moderate dyspnea and medium moist râles over both lungs from the spines of the scapulae to the bases, but no evidence of fluid in the chest. During the first part of his stay in the hospital he had signs of ascites. The heart was slightly enlarged. The vital capacity of the lungs was 2,000 cc. Electrocardiographic tracings were of the coronary type with a high origin of  $T_3$  and inverted  $T_1$  and  $T_2$ . There were left axis deviation and delayed auricular-ventricular conduction, the P R interval being 0.26 second. The blood pressure averaged 176 mm of mercury systolic and 100 mm of mercury diastolic. The basal metabolic rate was +3 per cent. On the continuation of a maintenance dosage of digitalis and rest in bed, the patient improved and was discharged. The diagnoses were chronic circulatory insufficiency, hypertensive cardiovascular disease, coronary arteriosclerosis, chronic cholecystitis and cholelithiasis. Operation for the last condition was not advised.

After discharge from the hospital, the patient felt fairly well on a somewhat restricted regimen until eight months before his present admission to the hospital, when he was forced to stay in bed for two months because of cough, dyspnea and weakness. For two months he attempted to supervise his business, but was forced to return to bed or to sit in a chair for the four months preceding his admission to the hospital. During the three weeks preceding entry, the edema of the legs and swelling of the ankles increased, orthopnea became pronounced, and sleep was broken because of dyspnea.

At the time of admission physical examination showed marked dyspnea and orthopnea, there were also deep cyanosis of the lips and mucous membranes, a moderately enlarged heart, no murmurs, sounds of fairly good quality, a gallop rhythm and a regular rate, 100 per minute. The arterial blood pressure was 180 systolic and 110 diastolic. Medium moist râles were heard from the spine of the scapula to the base over both sides except on the left side posteriorly, where signs of a moderate amount of fluid were evident. The abdomen was moderately distended owing to ascites. The tender edge of the liver was felt 3 fingerbreadths below the right costal margin. Moderate pitting edema of the lower part of the legs and of the hands and forearms was present.

Examination of the red and white cells of the blood gave normal results. Chemical analysis of the blood likewise gave normal results except for an icteric index of 25, which became normal after a few days of rest in bed. The electrocardiographic tracings showed normal sinus rhythm and delayed conduction, the P R interval varying from 0.24 to 0.30 second on different occasions.

Xanthine and mercurial diuretics were given repeatedly during the first twelve days, and the patient's weight decreased from 148 to 124 pounds (67.1 to 56.2 Kg), his state of nutrition remaining approximately the same. In order to estimate the rate of gain of the edema during rest in bed, the patient was given no diuretics between the twelfth and thirty-first days, the rest of his regimen being unchanged. During this period of nineteen days, the gain of edema was progressive. His weight increased  $11\frac{1}{2}$  pounds (5.2 Kg), and edema of the legs reappeared. The vital capacity of the lungs was 1,200 cc. Because of the progressive gain of the edema in spite of all the usual measures, the possible therapeutic effects of thyroidectomy were offered to the patient. After the administration of diuretics, a subtotal thyroidectomy was performed, a minute posterior shell of the gland being left in each tracheo-esophageal sulcus. This operation was performed on Oct. 17, 1932, on the thirty-fifth day of the patient's stay in the hospital.<sup>4</sup> Grossly and microscopically, the gland was normal.

The patient's convalescence was uneventful. One week following the operation, the basal metabolic rate had dropped from +7 to -7 per cent, and the signs of fluid within the chest had cleared up, although medium moist râles were still audible at the bases. The edge of the liver was no longer palpable. There was no edema of the legs or of the sacrum. During the following forty-five days, the basal metabolic rate averaged -14 per cent, and the patient gained 8 pounds (3.6 Kg). During the nineteen days preceding operation, when the basal metabolic rate averaged 7 per cent, he had gained about 11 pounds (5 Kg). Part of the postoperative gain in weight was undoubtedly due to the increased intake of food, for he felt much better and ate a full diet. An x-ray picture of the chest showed marked clearing of the pulmonary fields and a decrease of 1 cm. in the transverse diameter of the heart. The lack of gain in edema was striking, for whereas he had craved fluids before operation and had been on a restricted intake of 1,500 cc. of fluid and a salt-poor diet, he was given 6 Gm. of salt in his diet following operation and was permitted to drink all the fluids he wished. In addition, he was permitted to be up and about the ward for most of the day instead of being in bed. This lessened tendency for the edema to progress was reflected by a marked improvement in the patient's symptoms. The vital capacity of the lungs, which had ranged from 1,350 to 1,700 cc. before operation, varied from 1,800 to 2,000 cc. after operation.

The definite improvement in the patient's clinical condition, accompanied by a fall in the basal metabolic rate from +7 to -18 per cent, was not fully maintained after about the fiftieth day following operation. The basal metabolic rate gradually rose approximately to zero, and he gained edema more rapidly than during the fifty days when his metabolic rate was lower. It should be noted that the rate of formation of edema, even during this latter period when he was up and about the ward practically the entire day, was not as great as that observed before operation when he was confined to bed. We felt that the rise in the basal metabolic rate was caused by the fact that the remaining thyroid tissue had undergone hyperplasia. The patient is accordingly being treated by

<sup>4</sup> This operation and those performed in the succeeding cases were carried out by Dr. David D. Berlin.

roentgen irradiation, for although there is evidence that roentgen rays are not destructive to normal glandular tissue, it is possible that hyperplastic regenerating tissue may be more sensitive

Although the patient's condition is not so good as during the period when his metabolic rate was lower, he is nevertheless greatly improved in comparison to his preoperative state. It was felt that it would be of interest to have him describe as clearly as possible his present condition and that before operation. When asked to state in what respects he felt worse and in what respects he felt better, the patient said that before operation he suffered with insatiable "terrible thirst," and was able to sleep fitfully only by the nightly use of sedatives, and that he was unable to walk because of shortness of breath and swelling and stiffness of the legs. Following operation, the craving for water entirely disappeared, and he experienced no difficulty in breathing or walking, though he was up and about the ward almost the entire day.

CASE 2—H. B., a man, 54, unemployed, entered Beth Israel Hospital on Nov 1, 1932, for the fifth time in two and a half years because of recurrent edema of the legs, pain in the right upper quadrant of the abdomen and shortness of breath. His last discharge from the hospital was six months before the present admission. The diagnoses were arteriosclerotic heart disease, auricular fibrillation, generalized arteriosclerosis and Paget's disease. During the interim the signs and symptoms of congestive failure had continued, and he had been confined to bed practically the entire time.

Physical examination showed cyanosis, orthopnea, a grossly irregular action of the heart and a greatly enlarged heart. The tender edge of the liver was palpable 1 handbreadth below the right costal margin, and there was moderately deep pitting edema over the lower part of the legs, the feet and sacrum. A moderate number of moist rales were heard over both lungs, particularly at the bases. Laboratory examinations of the blood, urine and stool gave no significant findings. The blood pressure was 140 systolic and 70 diastolic. A roentgenogram of the chest taken at a distance of 7 feet showed the transverse diameter of the chest to be 29.4 cm., and the transverse cardiac diameter, 22.1 cm. Electrocardiographic tracings showed auricular fibrillation and bundle branch block, the ventricular rate was 80 per minute. During the first eight days in the hospital, there was no loss of edema with the patient at rest in bed. Two cubic centimeters of mersalyl was then given. Following diuresis from the tenth to the twentieth day, the patient gained 3 pounds (1.4 Kg.) accompanied by a slight increase in the clinical signs of congestive failure. During his entire preoperative period, fluids were limited to 1,500 cc., and the diet contained approximately 4 Gm. of salt. The basal metabolic rate was determined repeatedly and was  $-4$  per cent. Mersalyl was again administered on the twenty-first day. On the twenty-third day (Nov 29, 1930), subtotal thyroidectomy was performed.

Convalescence was satisfactory. From the eighth postoperative day, when daily weighing was again resumed, to the eighteenth postoperative day, the patient's weight remained stationary, and he had no signs of increasing edema. The gradual loss of his extreme preoperative craving for water was striking. The vital capacity of the lungs averaged 1,500 cc., whereas it had averaged 1,200 cc. before operation, these averages represented the mean of several daily readings. The liver decreased appreciably in size and was definitely less tender, and the patient felt much more comfortable. This clinical improvement was paralleled by a fall in the basal metabolic rate from an average of  $-4$  per cent before operation to  $-15$  per cent.

Following this period, the patient again tended to gain edema, and the clinical course was not so favorable. The basal metabolic rate again rose to the preoperative levels. This change in the basal metabolic rate and in the clinical course was interpreted as being due, in all probability, to regeneration of the thyroid remnants, and roentgen therapy is now being carried out.

Case 3—G F, an unemployed cook, aged 52, entered Beth Israel Hospital complaining of shortness of breath, palpitation, constant sense of pressure over the chest and weakness. His past history showed that he had had diphtheria, scarlet fever and rheumatic fever at the age of 12. The attack of rheumatic fever in childhood forced him to remain in bed for three months. He had also had frequent recurrent attacks of sore throat and tonsillitis. He felt quite well until three years prior to the present entry when, while working, he experienced severe pain in the precordial region, which radiated to the left shoulder and down both arms to the tips of the fingers. He was extremely dyspneic. The symptoms were relieved by a hypodermic injection, and after three days in bed he returned to work. After two and a half months, however, he was forced to go to a sanatorium because of increasing dyspnea and weakness. Two and a half years before admission he left the sanatorium, feeling quite well except for a sense of pressure over his chest. He attempted to work, but, because of dyspnea and weakness he was again forced to go to bed. The foregoing symptoms gradually became more and more severe, although he refrained from work and rested most of the day. During the last two years, he had noticed a gradual increase of edema in the legs.

He entered this hospital in the ward service eight months before the present admission, and at that time the findings on physical examination were essentially as at present. A note by a visiting physician at that time stated that the prognosis was not good and that the patient would be a cardiac invalid for life. The patient's condition improved on rest in bed, so that on discharge three weeks later he had only a slightly enlarged liver and minimal pitting edema of the legs. On discharge the diagnoses were arteriosclerotic heart disease, auricular fibrillation, (?) rheumatic heart disease and emphysema of the lungs.

Because of the continued evidence of the signs and symptoms of congestive heart failure, he was discharged to the state hospital for chronic diseases, where he was allowed table and lavatory privileges. He had a recurrence of his orthopnea, edema of the legs, enlargement of the liver, attacks of precordial pain and constant sense of pressure over the chest. Later he went to the Bickur Cholim Hospital for chronic diseases, where his condition remained essentially unchanged. He was seen by us at the Bickur Cholim Hospital, and because of his prolonged invalidism, in spite of all known medical procedures the possibility of a total thyroidectomy was offered.

On the patient's entry to Beth Israel Hospital physical examination showed orthopnea, slight cyanosis of the lips and mucous membranes and marked enlargement of the heart, the apex impulse being seen and felt in the sixth interspace in the anterior axillary line. The heart sounds were grossly irregular but of fairly good quality. There was a soft blowing systolic murmur which partly replaced the first sound and which was best heard over the mitral area and transmitted toward the left axilla and the base of the heart. The pulmonic second sound was greater than the aortic second sound. A faint middiastolic murmur was heard just below and to the left of the nipple. No aortic diastolic murmur was heard. The tender edge of the liver was palpable 3 fingerbreadths below the right costal margin. There was definite pitting edema over the legs and the sacrum. The blood pressure was approximately 125 systolic and 60 diastolic.



There were scattered moist rales over both lungs, particularly at the bases. The apex and radial pulse rates were 64 per minute. A roentgenogram taken at a distance of 7 feet showed the total transverse diameter of the heart to be 17.4 cm, the transverse diameter of the chest was 29.5 cm. Electrocardiographic tracings showed auricular fibrillation, QRS waves of rather small amplitude and diphasic  $T_1$  and  $T_2$ . The vital capacity of the lungs was 2,000 cc. The basal metabolic rate was  $-1$  per cent. Routine examinations of the blood and urine gave normal results. The diagnoses were auricular fibrillation, congestive heart failure, mitral stenosis and regurgitation and (?) probably old healed coronary thrombosis.

During the patient's preoperative stay in the hospital of twenty-one days, the vital capacity of the lungs varied from 2,000 to 2,700 cc. The evidences of congestive failure decreased, although they did not disappear entirely, and the weight decreased  $3\frac{3}{4}$  pounds (17 Kg) following diureses caused by repeated injections of mersalyl. Because there was evidence of regeneration after subtotal thyroidectomy in the preceding two patients, a complete total thyroidectomy was performed on this patient on Dec 15, 1932, the parathyroid glands being spared. The patient had an uneventful convalescence. Eight days after operation the basal metabolic rate was  $-7$  per cent, two weeks after operation,  $-14$  per cent, and three weeks after operation  $-16$  per cent. During the four weeks from then until the time of writing, Feb 1, 1933 the basal metabolic rate has been approximately  $-28$  per cent. For the last four weeks he has been up and about the ward for increasing periods of time, until at the present writing he is up practically the entire day and helps about the ward in performing minor duties, such as serving trays.

The change in the patient's clinical condition has been conspicuous. Instead of being orthopneic, he now sleeps flat in bed, and his craving for water has entirely disappeared. Instead of gaining edema, as occurred previously when he got out of bed even for part of the day, he is now undertaking moderate exercise without showing any signs or symptoms of congestive heart failure. Whereas before operation even combing his hair or turning over in bed caused violent palpitation, he now states that for the first time in three years he is "unaware that he has a heart." The sense of thoracic compression with numbness and occasional pain in the left arm from which he has suffered continuously for three years has not been present for over four weeks. He no longer complains of perspiration, and during the last two weeks he has spontaneously asked to be discharged from the hospital in order that he may return to work. It is interesting to note that in spite of his lowered metabolism and a somewhat increased sensitivity to cold, he states that his mental processes are more acute than formerly. This we interpret as being due to the fact that he compares his present state with his state of grogginess during congestive heart failure. He states that he thinks as keenly as he did about three or four years ago. The vital capacity of the lungs is now 3,100 cc. This increase is significant and may be considered to be the result of lessened congestion of the lungs.<sup>5</sup> The transverse diameter of the heart is essentially the same as previously. There has been no significant change in the velocity of the blood flow.

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5 Means, J. H. Dyspnoea, *Medicine* **3** 309, 1924. Drinker, C. K., Peabody, F. W., and Blumgart, H. L. The Effect of Pulmonary Congestion on the Ventilation of the Lungs, *J. Exper. Med.* **35** 77, 1922. Blumgart, H. L., and Weiss, S. Studies on the Velocity of Blood Flow. V. The Physiological and the Pathological Significance of the Velocity of Blood Flow, *J. Clin. Investigation* **4** 199, 1927.

CASE 4—J L, a factory foreman, aged 51, complained of a squeezing pain in his chest and arms. His illness began in 1928. He first noticed that if he walked hurriedly this pressure pain would develop in his chest and extend down both arms and would last about five minutes. In addition, he had a different kind of discomfort which he called heart burn, which he had had for many years. It came on about two hours after meals and was relieved by sodium bicarbonate.

He was first seen as an ambulatory patient on May 26, 1931, and showed nothing striking on physical examination. The blood pressure was 148 systolic and 82 diastolic. The heart was not enlarged, and there were no murmurs. The rhythm was regular with an occasional premature beat. The first heart sound was slightly diminished in intensity. Examination of the lungs and abdomen gave negative results. The urine was normal. The vital capacity of the lungs was 4,000 cc. An electrocardiogram showed left ventricular preponderance and flat T waves in lead I.

The patient was regarded as having definite angina pectoris and probable duodenal ulcer. Glyceryl trinitrate gave him prompt relief from the attacks of pain in the chest. He was also told to take five small meals a day instead of his customary three meals.

When he was next seen on May 20, 1932, it was learned that his condition had remained the same until two months previously, when the attacks of angina became more severe. The results of physical examination were unchanged. Because his skin was somewhat moist, although there was no exophthalmos, thyroid enlargement or tremor, he was given 10 drops of compound solution of iodine once a day and 0.1 Gm of euphyllin (theophyllin ethylenediamine) three times a day. He was again seen on October 18. He had had practically no attacks all summer, but during the preceding month he had had to use one or two pills of glyceryl trinitrate a day because of recurrent attacks. The attacks also began to occur while he was at rest without making any effort.

He entered Beth Israel Hospital on October 23. The basal metabolic rate was +25 and +30 per cent. He had been taking iodine during the previous five months. It was decided that a subtotal thyroidectomy should be performed, although the only evidence of hyperthyroidism was the moist skin and slightly elevated metabolism. It was felt that whether the gland was pathologic or normal some good might result from the operation. Treatment with 10 drops of compound solution of iodine three times a day was therefore continued. The metabolic rate was +10 and 12 per cent on October 30, and on November 1, a subtotal thyroidectomy was performed, about one tenth of the gland in the tracheo-esophageal sulcus being left. On November 19, the basal metabolic rate was -5 per cent. The thyroid gland appeared normal to the surgeon, and the report of the pathologist was that the thyroid gland was normal grossly and microscopically.

The patient left the hospital on November 19, he returned to work, and has had no attacks of angina since the operation. The first improvement during the previous summer may have been due to the warm weather. It may also have been due to the iodine or to the euphyllin. The final disappearance of the angina during the winter could not have been due to any of these causes, and seemed to be the specific result of the thyroidectomy. He now not only has no anginal pain while at rest or during excitement, but has been able to walk distances without distress, which he had found impossible before operation.

## COMMENT

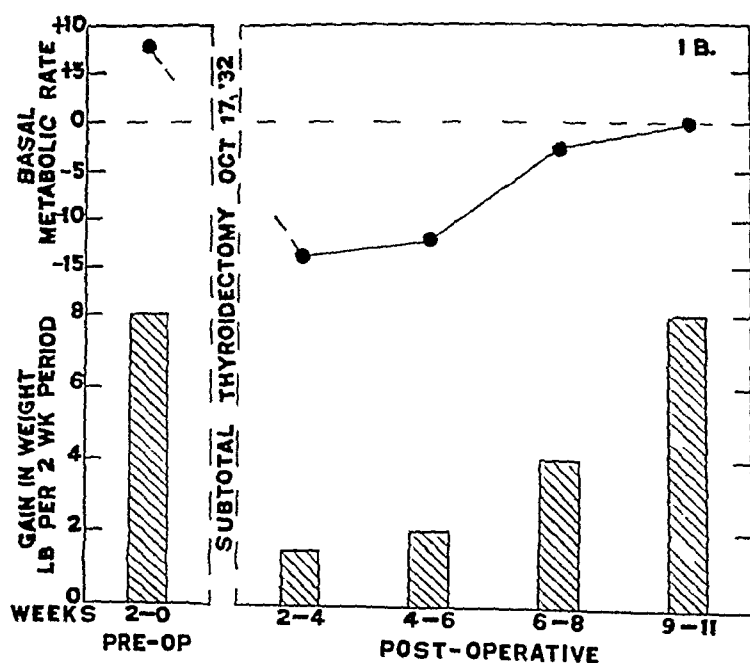
In evaluating the effects of any therapeutic procedure, one must guard against the possibility of suggestion or of spontaneous changes in the clinical course of the disease as accounting for the patient's improvement in symptoms. For this reason, patients have been selected for study whose clinical course has remained practically unchanged over a long time, and who have received medical evaluation of their condition from time to time before coming to the hospital.

In cases 1 and 2, subtotal thyroidectomy caused a fall in the metabolic rate, which reached its maximum about three weeks after operation. Clinical improvement paralleled the lowering of metabolism and was evidenced by the absence of edema, the increased vital capacity of the lungs and the ability to be up and about the ward without discomfort. During the next few weeks, the basal metabolic rates in these two patients again rose toward the preoperative normal level, and the clinical conditions became less favorable. The patient in case 1 continued for an additional month to show a metabolic rate somewhat lower than before operation, and his clinical condition, while not as good as that three weeks following operation, was definitely better than before operation. Before operation, accurately controlled observations over a period of five weeks showed that even while he rested in bed he gained edema spontaneously at the rate of about 5 pounds (2.3 Kg.) a week. During the latter part of the study he was up and about the ward for most of the day and was no longer orthopneic, and in spite of his markedly increased activity he did not have as rapid a gain of edema as before operation (chart). This is in pronounced contrast to his clinical state before operation, when he was forced to remain in bed at home continuously for more than eight months.

Because the metabolic rate of these two patients did not remain persistently lowered, it was decided to perform total thyroidectomy on the third patient. The parathyroid glands were identified, and total ablation of all thyroid tissue was done. The patient had an uneventful convalescence, and about six weeks after operation had a basal metabolic rate ranging from  $-25$  to  $-30$  per cent. At the time of writing he is up and about the ward practically the entire day, feels strong, is no longer orthopneic, has absolutely no signs of congestive heart failure and is eager to leave and return to work. The fact that this patient showed no such change while in hospitals for the care of patients with chronic diseases during the last two and a half years and no improvement after all the usual medical measures had been invoked under our observation makes us confident that the striking change in his clinical condition can safely be attributed to the sustained lowering of the basal metabolic rate effected by total ablation of the thyroid.

The patient states that whereas previously even combing his hair or turning over in bed was attended by severe palpitation, he no longer suffers from such distress. For the first time in years he is able to sleep lying flat in bed. The sense of substernal oppression from which he had suffered for three years has disappeared.

The fourth case deserves special comment. The patient had been suffering from typical angina pectoris for four years. He lacked all the classic evidences of hyperthyroidism, such as exophthalmos, palpitation, enlargement of the thyroid gland, tremor, nervousness, loss of weight or increase in the velocity of the blood flow. The basal metabolic rate, however, was slightly elevated, being about 25 per cent,



Relation between the lowered basal metabolic rate and the rate at which edema formed in the patient in case 1 while he was at rest in bed

and the skin was moist. He might have been regarded as having a case of masked hyperthyroidism,<sup>6</sup> but when the thyroid gland was removed it was found to be normal. The metabolism was definitely lowered by the operation, and with this the anginal attacks disappeared.

Studies of the velocity of the blood flow in these patients show that in spite of clinical improvement the speed of the blood flow remains the same as that previous to operation. It appears, therefore, that we

6 Levine, S. A., and Sturgis, C. C. Hyperthyroidism Masked as Heart Disease, *Boston M & S J* **190** 233, 1924. Levine, S. A., and Walker, G. L. Further Observations on Latent Hyperthyroidism Masked as Heart Disease Angina Pectoris, *New England J Med* **201** 1021, 1929. Levine, S. A. Unrecognized Hyperthyroidism Masked as Heart Disease, *Ann Int Med* **4**:67, 1930.

have not altered the fundamental state of the circulation. In terms of the law of supply and demand, we may say that the supply of the blood has not been increased, but the demands have been reduced to such an extent that the reduced supply is now adequate to the ordinary needs of daily life under these new circumstances. The latter considerations add further confirmation to the fact that the improvement may be attributed to the effects of thyroidectomy. In an extensive series of patients with cardiac disease whose velocity of blood flow was studied, it was found that when clinical improvement occurs under the usual medical procedures, the metabolic rate presumably remaining unchanged, the clinical improvement is attended by an increased speed of blood flow.<sup>7</sup> Further studies are being made in order to appraise the value of thyroidectomy and the effect of roentgen irradiation more accurately. Until this is accomplished, the operation is indicated in only a relatively small group of patients who have been observed over a considerable period of time, for, as is well known, the natural course of cardiovascular disease is often irregular. Advanced arteriosclerosis, impaired renal function, syphilitic cardiovascular disease, active rheumatic infection or active phases of acute coronary thrombosis are adverse factors. Similarly, if the course of the disease seems rapidly progressive, operation is obviously contraindicated. In performing thyroidectomy, injury to the parathyroid glands must be avoided. The special surgical details which must be observed will be given in a forthcoming communication. The application of this procedure to other conditions in which a lowering of the metabolic rate may prove to be beneficial is also being studied. In the meantime, the procedure should be employed only in carefully selected cases in which all known therapeutic measures have proved ineffectual.

#### SUMMARY

Reasons are given for believing that patients with a normal metabolism who suffer from congestive heart failure or angina pectoris might show striking improvement if the metabolic rate were significantly lowered. The hearts of such people might be unable to supply enough blood for the ordinary demands of a normal metabolic rate, but nevertheless might be able to supply enough blood for a reduced metabolic rate. The present communication reports the results of producing a subnormal metabolic rate by thyroidectomy on three patients who were suffering from severe congestive heart failure but who showed no

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<sup>7</sup> Blumgart, H. L. The Velocity of Blood Flow in Health and Disease. The Velocity of Blood Flow in Man and Its Relation to Other Measurements of the Circulation, *Medicine* 10 1, 1931.

evidences of disturbed thyroid function, and on one patient with angina pectoris with a slight elevation of metabolism but with a normal gland. In the patients studied the signs and symptoms of circulatory insufficiency and of angina pectoris had persisted for a considerable time in spite of all known medical procedures. The clinical condition of each patient was accurately studied during a long control period in order that any change following thyroidectomy could be attributed confidently to the effect of the procedure.

In two of the three patients with severe congestive heart failure subtotal thyroidectomy caused a fall in the metabolic rate which reached its maximum about three weeks after operation. Clinical improvement paralleled the lowered metabolism and was evidenced by the disappearance of edema, the increased vital capacity of the lungs and the ability to be up and about the ward without discomfort. During the next few weeks, the basal metabolic rates in these two patients again rose toward the preoperative normal level, and their clinical conditions became less favorable. One of these patients continued for an additional month to show a somewhat lessened metabolic rate than before operation, and his clinical condition, while not so good as that three weeks following operation, was definitely better than before operation. The patient with angina pectoris has shown no recurrence of the attacks of angina pectoris since subtotal thyroidectomy, although he has returned to work and active life. This is in contrast to his condition before operation, when attacks of angina pectoris occurred even while he was at rest.

In one patient with congestive heart failure complete ablation of all thyroid tissue was done, the parathyroid glands being spared. This patient has maintained his conspicuous clinical improvement and the metabolic rate has remained persistently lowered for more than six weeks. Further studies are being made in order to appraise the value of thyroidectomy and the effect of roentgen irradiation more accurately. The application of this procedure to other conditions in which a lowering of the metabolic rate may prove beneficial is also being studied. In the meantime, the procedure should be employed only in carefully selected cases in which all known therapeutic measures have proved ineffectual.

# NATURE OF SKIN REACTIONS PRODUCED BY HEAT-INACTIVATED POLIOMYELITIS VIRUS

REACTION OF PERSONS CONVALESCING FROM POLIOMYELITIS AND OF  
NORMAL PERSONS TO INTRACUTANEOUS INJECTIONS OF  
THE HEAT-INACTIVATED VIRUS

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The purpose of the present investigation was to determine whether or not persons who had recovered from poliomyelitis or those who are generally considered resistant to it possess any cutaneous allergy to the heat-inactivated virus of the disease. Our aim, obviously, was to devise a skin test which would differentiate between susceptibility and resistance to poliomyelitis on a specific immunologic basis. Although there are no known manifestations of the human disease which suggest the operation of an allergic mechanism, the extensive study of experimental poliomyelitis in monkeys has brought forth various observations for which hypersensitiveness or allergy to the virus has been considered as one of the possible explanations by certain investigators<sup>1</sup>. Recently, one of us (C W J<sup>2</sup>) showed that monkeys that have recovered from experimental poliomyelitis respond with an accelerated rise of temperature to an intracranial or subcutaneous injection of the virus, and interpreted this phenomenon as a specific, allergic, febrile reaction. The possible practical application of this observation

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1 Roemer, P. H. Epidemic Infantile Paralysis, English translation, New York, William Wood & Company, 1913. Shaughnessy, H. J., Harmon, P. H., and Gordon, F. B. The Resistance to Poliomyelitis of Animals Previously Inoculated with Heated Virus, *J. Prev. Med.* **4** 157, 1930. Brebner, W. B. Evidence of Possible Occurrence of Anaphylactic Phenomena in Poliomyelitis Immune Monkeys, *Proc. Soc. Exper. Biol. & Med.* **29** 351, 1932.

2 Jungeblut, C. W. An Accelerated Febrile Reaction in Monkeys Upon Reinoculation with Poliomyelitis Virus, *J. Exper. Med.* **53** 159, 1931.

led to an investigation of the reaction of persons convalescing from poliomyelitis to the injection of heat-inactivated poliomyelitis virus. Preliminary tests<sup>3</sup> on twenty-seven children and youths with residual paralysis showed that all of them responded with a delayed skin reaction (maximum development in twenty-four hours) at the site of the intracutaneous injection of heat-inactivated virus.

The recent epidemic of poliomyelitis in New York City and vicinity stimulated a more extensive and critical study of this problem. The plan involved the testing of a certain number of persons convalescing from poliomyelitis and normal adults who generally are known to have a high resistance to the disease, and comparison of their skin reactions with those obtained in normal children of the susceptible age groups. The investigation as originally planned also included a study of similar tests on patients in various stages of acute poliomyelitis.

#### NATURE OF PREPARATIONS USED FOR INTRACUTANEOUS TESTS

The virus-containing solutions were prepared from the spinal cords of monkeys with typical experimental poliomyelitis, for control, similar extracts were prepared from the spinal cords of normal monkeys. The cords, which were preserved in glycerin for varying periods of time after their removal, were ground up with sand and physiologic solution of sodium chloride, and 5 per cent suspensions were prepared in the usual manner. After centrifugation, the supernatant liquid was heated at 65 C for one hour, which is more than sufficient to inactivate the virus completely. During the heating a flocculent precipitate appeared in most preparations, after filtration through a Seitz or a Berkefeld N filter, the solutions were tested for sterility by culture and for the absence of active virus by intracranial injection into monkeys. Except when otherwise indicated, the solutions were not used until two or more months after their preparation. In tests 1, 2 and 7, the Aycock-1916 strain of virus was used, in the other tests, the mixed Rockefeller Institute virus and our own 1931 human virus were used in addition to the Aycock strain.

#### DESCRIPTION OF THE INTRACUTANEOUS TESTS

Two-tenths cubic centimeter of the various solutions was injected intracutaneously into the flexor surface of the forearms. The site of inoculation was usually observed for about half an hour after injection, and then after from six to eight hours, and again after twenty-four hours. In a few sensitive persons an immediate urticarial reaction

<sup>3</sup> Jungeblut, C. W. Allergic Reactions in Polio-Convalescent Children After Intracutaneous Injection of Heat-Inactivated Poliomyelitis Virus, *Proc Soc Exper Biol & Med* 28:1072, 1931.



occurred with both the virus cord and the normal cord preparations, these reactions disappeared completely within from two to three hours. Positive, delayed reactions consisted of edema and erythema of varying degree. The extent of the reactions was measured in millimeters, those that were less than 10 by 10 mm were not considered positive for the purpose of this paper. While this practice eliminated a certain number of weak reactions, an arbitrary line in recording the results had to be drawn somewhere for purely practical reasons.

TABLE 1—*Skin Reactions of Persons Convalescing from Poliomyelitis and of Normal Children and Youths\**

Name	Age, Years	Interval Since Onset of Paralysis, Years	Monkey, Polio Cord		Monkey, Normal Cord	
			24 Hours	36 Hours	24 Hours	36 Hours
K I	6	5	0	0	0	0
T O †	16	15	0	+	0	0
V D R †	16	2	++	+	0	0
M N †	23	16	++	+++	0	0
P C †	15	14	+	0	0	0
F O †	16	4	0	0	0	0
E R	2	1	0	0	0	0
D B †	15	14	0	0	0	0
T G	4	?	0	0	0	0
E E	10	8	0	0	0	0
M H	13	8	+	0	0	0
H P	2	?	0	0	0	0
A O	2	1	0	0	0	0
E D	16	No history of poliomyelitis	0	0	0	0
O W	11		0	0	0	0
O B	10		0	0	0	0
A G	13		+	++	0	0
L M	10		0	+	0	0
A B	15		0	0	0	0
L P	10		+	0	0	0
B H	10		0	0	0	0
O R	14		0	0	0	0
R B	15		0	0	0	0
E L R	8		++	++	0	0
F T	9		++	++	0	0

\* No reaction or slight redness up to 9 × 9 mm = 0. Redness 10 × 10 mm to 19 × 19 mm = +. Redness 20 × 20 mm to 29 × 29 mm = ++. Redness 30 × 30 mm to 39 × 39 mm = +++.

† Serum failed to neutralize virus in vitro.

‡ Serum neutralized virus in vitro.

1 *Skin Reactions of Children and Youths Convalescing from Poliomyelitis and of Normal Subjects*—In this test, thirteen children and youths convalescing from poliomyelitis, with residual paralysis for periods varying from one to sixteen years, and twelve who had no history of poliomyelitis were given injections of a heat-inactivated preparation of monkey virus and a similar preparation of normal monkey cord (table 1). Whereas none reacted to the normal monkey cord, four from each group exhibited positive skin reactions with the virus. However, the incidence of clearcut positive reactions was so low, when compared with the uniformly positive results observed in the preliminary test, that it appeared to be due to a diminished concentration of the reaction-producing principle. Whether or not this variation depended on a decreased concentration of virus was neither clear nor definite.

2 *Skin Reactions of Persons Convalescing from Poliomyelitis and of Normal Adults and Young Children*—The purpose of this test was to observe the effect of other preparations of virus and normal monkey cords, and to compare the reactions of persons convalescing from poliomyelitis with those of normal adults and young children (table 2)

TABLE 2—*Skin Reactions of Persons Convalescing from Poliomyelitis and of Normal Adults and Young Children* \*

Group	Name	Age, Years	Monkey, Polio Cord		Monkey, Normal Cord	
			7 Hours	24 Hours	7 Hours	24 Hours
Persons convalescing from poliomyelitis	L V †	7	+	0	+	0
	Gr †	19	+	+	0	0
	P C †	19	+	0	+	0
	Kl	16	0	+	0	0
	Cr ?	15	0	+	+	0
	Rl †	18	+	+	+	0
	Po	18	+	++	0	0
	Ru	13	0	0	0	0
	De	9	+	+	0	0
	Ge	9	+	+	+	+
	D B †	15	+	0	+	0
	M H	13	+	+	+	+
	F M †	12	+	+	0	0
	M S	13	0	0	0	0
	L R	?	++	++	0	+
	P O †	15	0	0	0	0
	B L	?	0	+	0	0
	F O †	16	0	0	0	0
	A B	19	0	+	0	0
	E E	10	0	0	0	0
No history of polio myelitis	Co	From 20 45 years of age	+	0	+	0
	Ju †		+	+	++	+
	Fr †		+	+	+	+
	HA		++	++	++	+++
	Cl		++	++	++	++
	Ho		++	+	++	+
	St		+	0	+	0
	In		0	0	0	0
	Sa		+	0	+	++
	En		++	0	++	+
	Bu †		+	0	+	0
	To		+	+	+	+
	Jo		+	0	+	0
	St		0	++	0	++
	Se		0	0	0	0
	Ka		0	++	0	0
	Ga		++	+	++	+
No history of polio myelitis	A S	3 weeks				
	J M	1 month				
	R W	1 month				
	J S	1 month				
	N A	1 month				
	L Y	6 months				
	M N	1 year				
	E L	1 year				
	W D	2½ years				
	M D	2½ years				
	E A	2¾ years				
	B L	2¾ years				
	F S	3 years				
	E B	3½ years				
	P B	5 years				
	M S	6 years				
	O N	6½ years				
	N S	7 years				
	D W	8 years				
	O L	8 years				
	R O	9½ years				
	F D	10 years				
			All negative		All negative	

\* No reaction or slight redness to  $9 \times 9$  mm = 0 Redness  $10 \times 10$  mm to  $19 \times 19$  mm = +  
Redness  $20 \times 20$  mm to  $29 \times 29$  mm = ++ Redness  $30 \times 30$  mm to  $39 \times 39$  mm = +++  
Redness  $40 \times 40$  mm to  $49 \times 49$  mm = ++++

† Serum failed to neutralize virus in vitro

‡ Serum neutralized virus in vitro

In a group of twenty convalescents (varying in age from 7 to 19 years), after the injection of the virus solution there were ten slightly positive reactions and two more strongly positive ones at the end of twenty-four hours, in the same group, only three persons showed slightly positive reactions to the preparation of normal monkey cord twenty-four hours after injection, while seven had reacted to the control material at the earlier reading. In the group of seventeen normal adults, the ages varying from 20 to 45 years, there were five slightly positive and four strongly positive reactions to the virus-containing solution at the end of twenty-four hours, but practically just as many and as severe reactions to the control solution prepared from normal monkey cord. The latter positive reactions, which were indistinguishable from those obtained with the virus solution, naturally raised the question whether there is any specific difference between the reaction-producing principles in the two solutions. It appeared rather as though the reactions were complicated by some peculiarity in the skin of different persons, there being a tendency with increasing age to react more markedly to either of the two products. Thus it will be seen that none of the group of twenty-two normal children (varying in age from 3 weeks to 10 years) who were given injections of the same material showed any positive reactions at the end of twenty-four hours to either the virus or the control solution. However, even if one should be inclined to regard the positive skin reactions of the persons convalescing from poliomyelitis and of some normal adults as specific allergic reactions to the virus, the failure to obtain such reactions in all of the young children is not in good agreement with the expected number of susceptible subjects among them.

3 *Skin Reactions of Normal Adults and of Adults Convalescing from Poliomyelitis to the Mixed Rockefeller Institute Monkey Virus and the 1931 Virus Derived from Human Spinal Cords*—Since certain preparations of normal monkey cords gave skin reactions that were indistinguishable from those produced by the virus solutions, the proper interpretation of the test became very confusing. Moreover, the irregularity with which virus solutions elicited these skin reactions in persons convalescing from poliomyelitis called for more extensive tests with various poliomyelitis monkey cord preparations.

The mixed Rockefeller Institute virus, which had undergone numerous monkey passages in the Research Laboratories of the New York City Department of Health, was used in this test. The preparation was passed through a Seitz filter, and before heating as little as 0.05 cc produced typical poliomyelitis in a monkey. Since in most of the other preparations a flocculent precipitate formed during the heating, there was no certainty as to how much of the virus actually remained in the

clear solution, in the present preparation, however, no flocculent precipitate formed, so that one could feel assured of a definite content of heat-inactivated virus. A new extract of normal monkey cord was prepared in the same manner. Largely to eliminate the factor of "foreign protein" and to use the virus before it had been adapted to monkeys, extracts were prepared from suitable pieces of the spinal cords from three patients who died of poliomyelitis in 1931, before heating, the emulsion produced typical poliomyelitis in monkeys. This test differs from previous tests also in the fact that all of the solutions were used three days after their preparation.

Fourteen normal adults, four persons convalescing from poliomyelitis with residual paralysis and three who gave histories of so-called

TABLE 3—*Skin Reactions of Normal Adults and of Adults Convalescing from Poliomyelitis to the Mixed Rockefeller Institute Monkey Virus and the 1931 Virus Derived from Human Spinal Cords*

Name	Age, Years	History of Poliomyelitis	Monkey, Normal Cord	Monkey, Polio Cord, Mixed Virus	Human, Polio Cord, 1931 Virus
A L	21	None	All negative	All negative	All negative
H F	22				
A S	26				
S G F	24				
H N	20				
N S	24				
A G	20				
E K	23				
O S	22				
W B	32				
A O	22				
W	28				
J W	20				
B S	30				
C N P	30	"Abortive" poliomyelitis? in 1916	Negative	Negative	Negative
L A L	20				
W H	28				
J J D	21	Paralysis 1909 Paralysis 1916 Paralysis 1906 Paralysis 1916	Negative	Negative	Negative
F A	24				
C J	30				
J H	18				

"abortive" poliomyelitis in 1916 were tested with these solutions (table 3). In view of the nature of the preparations, it was most interesting to observe that at from eighteen to twenty-four hours there was not a single positive skin reaction. While a different strain of virus was used in this test and the number of authentic subjects convalescing from poliomyelitis was small, the absence of any reactions with preparations known to contain definite quantities of heat-inactivated virus is difficult to reconcile with the existence of a widespread cutaneous allergy to the heat-inactivated virus of poliomyelitis.

4 *Skin Reactions of Young Children with Poliomyelitis Early After the Onset of Paralysis*—The purpose of this test was to determine whether or not soon after the onset of paralysis young children

would react differently from older convalescent and normal persons. This test was conducted simultaneously with test 3, and the same solutions were used, in addition to these, an older preparation (about 5 months old), which was used in test 2, was included for comparison. Twelve children, varying in age from 9 months to 10 years, were given injections. They all had definite paralytic involvement, the interval since the onset of paralysis varying from four to eighteen days. With the exception of one child who had received antipoliomyelitic horse serum, none had had any serum therapy. As is indicated in table 4, there was not a single positive reaction in from eighteen to twenty-four hours. The results of this test, however, while in perfect agreement

TABLE 4—*Skin Reactions of Young Children Suffering from Poliomyelitis Early After the Onset of Paralysis*

Name	Age	Serum Therapy	Days Since Onset of		Human Polio Cord, 1931 Virus	Monkey Polio Cord, 1916 Virus	Monkey Polio Cord Mixed Virus	Monkey Normal Cord, No Virus
			Symp toms	Paralysis				
J. P.	9 mos	None	17	14	All negative	All negative	All negative	All negative
M. Y.	18 mos	Antipoliomyelitic horse serum	16	14				
A. C.	22 mos	None	12	11				
T. H.	2½ yrs	None	9	8				
G. A.	3 yrs	None	?	11				
E. M.	4 yrs	None	7	6				
P. L. S.	4 yrs	None	?	12				
J. M.	4 yrs	None	13	13				
S. R.	5 yrs	None	?	11				
G. G.	6½ yrs	None	15	12				
C. M.	8 yrs	None	4	4				
J. H.	10 yrs	None	?	18				

with those of test 4, should not be interpreted without some reservation, since allergy may conceivably not have developed so early in the course of the disease.

5 *Skin Reactions of Older Persons Convalescing from Poliomyelitis to Human and Monkey Strains of Virus*—This test was conducted in order to observe the reactions of a larger group of older persons convalescing from poliomyelitis to the solutions employed in tests 3 and 4 after they had been kept in the icebox for two months. Five normal adults, two of whom had reacted negatively before in test 3, were given injections of the preparations the day before they were used on the persons convalescing from poliomyelitis, it is interesting to note that one of the solutions (mixed virus cord) induced some doubtful and some slightly positive reactions, practically all of which, however, disappeared within twenty-four hours. Among the twenty-three subjects convalescing from poliomyelitis, there were at the end of twenty-four hours from five to seven positive reactions of varying intensity with either of the two monkey virus preparations as contrasted with a single

positive reaction with the human virus cord. Moreover, three delayed reactions were noted with the normal cord solution in the latter group. The impression was gained that in this test all the preparations, though to a lesser extent than the normal cord, contained some reaction-inciting principle to which the skins of only some persons responded.

*6 Skin Reactions of Persons Convalescing from Poliomyelitis and of Adults to Preparations from Monkey Spinal Cords Preserved by Various Methods*—The results obtained in the preceding tests sug-

TABLE 5—*Skin Reactions of Older Persons Convalescing from Poliomyelitis to Human and Monkey Strains of Virus\**

Name	Age, Years	Interval Since Onset of Paralysis, Years	Monkey, Normal Cord, No Virus		Monkey, Polio Cord, Mixed Virus		Monkey, Polio Cord, 1916 Virus		Human, Polio Cord, 1931 Virus	
			6 Hrs	24 Hrs	6 Hrs	24 Hrs	6 Hrs	24 Hrs	6 Hrs	24 Hrs
Cr †	15	14	0	0	±	0	±	0	0	0
K	9	7	0	0	±	0	±	0	0	0
S			0	0	±	0	±	0	0	0
O †	16	15	0	0	±	+	±	0	0	0
Cu	12		0	0	0	0	0	0	0	0
A	11		0	0	0	0	0	0	0	0
Co	9	6	0	0	0	±	0	+	0	0
D	4		0	0	0	±	0	0	0	0
A			0	0	±	0	±	0	0	+
Bi	5		0	±	0	±	0	±	0	0
Sa	3		0	±	0	0	0	0	0	0
H	13	6	0	0	+	0	+	±	0	0
G	9	7	0	+	0	0	0	0	0	0
Ga	7	6?	0	0	0	++	0	+	0	0
Th			0	0	0	0	0	0	0	0
Ort †	16	4	0	0	0	0	0	+	0	0
Ba	19	18	0	0	0	0	0	0	0	0
Ko	16	14	0	0	0	0	0	0	0	0
Fi †	13	3	0	0	0	0	0	0	0	0
Et	10	9	+	0	0	0	0	±	0	0
Ge	9	2	0	0	0	0	0	±	+	0
Pa			0	0	0	0	0	0	0	0
Kl	17	10, 16	0	0	0	0	0	0	0	0
Go §	10	No	±	0	+	++	+	+	0	0
D B	27	history	0	0	+	+			0	0
A L	21	of	0	0	±	0			0	0
B G	18	polio	0	0	±	0			0	0
B B	27	myelitis	0	0	+	0			0	0
B S	30		0	0	+	0			0	0

\* No reaction or very slight redness to  $9 \times 9$  mm = 0  $10 \times 10$  mm to  $19 \times 19$  mm = ±  
Very faint or faint redness

$10 \times 10$  mm to  $19 \times 19$  mm = + Definite edema and erythema

$20 \times 20$  mm to  $29 \times 29$  mm = ++ Definite edema and erythema

† Serum failed to neutralize virus in vitro

‡ Serum neutralized virus in vitro

§ Clinically not poliomyelitis, congenital spastic paraplegia

gested a possibility that the positive reactions produced by some of the preparations might have been due to autolytic or other cord decomposition products which they contained. Thus it seemed advisable to compare the effect of solutions prepared in the routine manner, i. e., from spinal cords preserved in glycerin, with that of solutions prepared from freshly removed, unpreserved cords.

Two spinal cords were obtained from monkeys with typical poliomyelitis, without any preliminary contact with glycerin, one cord was

processed immediately, the preparation being known as "fresh polio cord", the other was dried in a desiccator to constant weight and then used for the preparation of the solution known as "dried polio cord". Another spinal cord was removed from a healthy, normal monkey and dried similarly in a desiccator, and the solution prepared from it was designated as dried normal cord. In addition to these three solutions, two others were prepared in the routine manner, i. e., one from pooled, glycerinated, poliomyelitic monkey cords, and the other from a glycerinated normal monkey cord.

TABLE 6—*Skin Reactions of Persons Convalescing from Poliomyelitis and of Normal Adults to Preparation from Monkey Spinal Cords Preserved by Various Methods*

Name	Age, Years	Interval Since Onset of Paralysis	Pooled Polio Cords		Glycerin Polio Cords		Fresh Polio Cord		Dried Polio Cord		Dried Normal Cord		Glycerinated Normal Cord	
			6 Hrs	24 Hrs	6 Hrs	24 Hrs	6 Hrs	24 Hrs	6 Hrs	24 Hrs	6 Hrs	24 Hrs	6 Hrs	24 Hrs
Ko	16	14	0	0	0	0	++	++	+	0	0	0	0	0
Th	15	13	0	0	0	0	++	++	0	0	0	0	0	0
Ba	21	5	0	0	+	0	++	+	0	0	0	0	0	0
Ke	16	1	0	0	0	0	0	0	0	0	0	0	0	0
Hu	14	6	0	+	+	—	++	+++	+	0	+	0	+	0
Or †	17	5	0	0	0	0	++	+	0	0	+	0	+	0
Ke †	9	7	0	0	0	0	++	+	0	0	0	0	0	0
Co †	16	15	0	0	0	0	+	+	0	0	0	0	0	0
Ki	17	10, 16	0	0	0	0	+	++	0	0	0	0	0	0
Ot	21	1	0	0	0	0	+	++	0	0	0	0	0	0
Bu †		No history of polio myelitis					0	0	0	0				
Va †							+	±	0	0				
Fo							0	++	0	0				
Kl †							0	0	0	0				
Cu							0	++	0	0				
De							+++	+++	+	0				
Sch							++	++++	++	++				

\* See table 2 for interpretation of signs

† Serum neutralized virus in vitro

‡ Serum failed to neutralize virus in vitro

Within four days after their preparation, the solutions were injected into seven normal adults and ten persons convalescing from poliomyelitis, many of whom had been used in previous tests. When one compares the three "polio" preparations (table 6), one finds that only one of the ten convalescents gave a slightly positive reaction to the glycerinated "polio" cords and the fresh "polio" cord, respectively, whereas nine of the ten convalescents and five of the normal persons reacted more or less strongly to the dried "polio" cord. Although, with one exception, there were, at twenty-four hours, no positive reactions with any of the normal cord preparations, it is difficult to regard the results obtained with the dried "polio" cord as evidence of an allergic response to the virus, since no such reactions were obtained with the two other "polio" preparations. There is, of course, a possibility that primarily toxic substances originating from the poliomyelitic lesions were present in the dried polio cord in unusual quantities, in view of the fact that certain

toxic factors have recently been described by Toomey<sup>4</sup> in the stool and urine of patients with poliomyelitis. However, similarly acting toxic substances had been derived from normal cords as well in other tests. It is for this reason that no single normal cord preparation can properly constitute a control.

*7 Skin Reactions with Concentrated Preparations Derived from Poliomyelitic and Normal Monkey Cords*—This test was conducted for the purpose of observing the reactions which would be elicited by purified and concentrated preparations. A method developed by one of us (A. B. S.<sup>5</sup>) enabled a partial purification and concentration of the virus. The solution prepared for this test was sufficiently potent (before heating) so that only 0.0003 cc produced typical poliomyelitis in a monkey; it was apparently protein free, gave negative biuret, xanthoproteidic and ninhydrin reactions and contained only 0.04 mg of nitrogen per cubic centimeter. For control, the spinal cords were removed from four healthy, normal monkeys and passed through precisely the same procedures for purification and concentration to which the poliomyelitic cords were submitted.

One-tenth cubic centimeter of each of the concentrated solutions was injected intracutaneously into four normal volunteers. The injections were attended by a great deal of pain which lasted only as long as the solution was being forced in from the syringe. Secondary sodium phosphate ( $\text{Na}_2\text{HPO}_4$ ), which was used for extraction in the process of purification, gives similar intense pain on intracutaneous injection, and since small amounts of it might have remained in spite of the prolonged dialysis of the solutions, one hundred and fiftieth molar  $\text{Na}_2\text{HPO}_4$  was injected as an additional control. The reactions (table 7) to the preparations derived from both the poliomyelitic and the normal cords were the most severe of any seen in the various tests; marked edema and erythema occurred, which at twenty-four hours was, on the average, about 40 mm in diameter. That these reactions were not due to  $\text{Na}_2\text{HPO}_4$  only is evident from the comparatively slight and transitory effect of the salt alone, and from the fact that after further dialysis of these solutions, reactions of the same intensity were produced on reinjection. The nature of the substance responsible for these particular reactions is unknown, the normal cord control having eliminated the virus as a factor. Although the final solutions were sterile, neither aseptic nor antiseptic conditions prevailed at the various stages of their preparation, and contamination

4 Toomey, J. A. Presence of a Specific Toxic Factor in the Stools and Urines of Poliomyelitis Patients, *Proc Soc Exper Biol & Med* **29** 866, 1932.

5 Sabin, A. B. Experiments on the Purification and Concentration of the Virus of Poliomyelitis, *J Exper Med* **56** 307, 1932.



with organisms in the an occurred, it is, therefore, not improbable that certain soluble bacterial products may be contained in them. However, whether soluble bacterial substances or spinal cord decomposition products are responsible for these reactions is not clear. Tests with suspended strips of the uterus of guinea-pigs revealed no histamine-like bodies.

#### SUMMARY AND COMMENT

The tests reported in this article were begun with the object of determining whether or not persons who are resistant to poliomyelitis would react differently to an intracutaneous injection of heat-inactivated virus from those who are known to be relatively more susceptible. Groups of adults and children who had no history of poliomyelitis were tested and compared with groups of persons convalescing from polio-

TABLE 7—*Skin Reactions to Concentrated Preparations Derived from Poliomyelitic and Normal Monkey Cords*

Name	Age, Years	Partially Purified and Concentrated		M/150 Na <sub>2</sub> HPO <sub>4</sub> , Mm	
		Monkey Polio Virus, Reaction in Mm	Normal Monkey Cord, Reaction in Mm	6 Hours	24 Hours
G O	18	45 × 35	50 × 40		
L E	21	40 × 30	55 × 45		
S A	26	30 × 30	50 × 40	20 × 15	10 × 10
B O	27	35 × 30	40 × 30	20 × 20	12 × 12

myelitis, among whom the interval since the onset of paralysis varied from four days to twenty-four years. The solutions used in these tests were sterile, heat-inactivated extracts derived from poliomyelitic monkey and human spinal cords and, for control, from the spinal cords of healthy, normal monkeys.

In some of the tests certain normal adults and persons convalescing from poliomyelitis gave positive, delayed (maximum development in from eighteen to twenty-four hours) skin reactions with preparations containing heat-inactivated virus and no reactions with similar preparations of normal cords, which appeared at first like a specific allergic response of persons who are resistant to poliomyelitis. However, after more tests had been conducted many preparations were encountered which, in spite of the fact that they were definitely potent as far as their content of heat-inactivated virus was concerned, failed to give any positive reactions. This observation naturally threw considerable doubt on the interpretation of the positive skin reactions as manifestations of specific, cutaneous allergy to the heat-inactivated virus, this doubt was further strengthened when it was found that certain preparations derived from normal cords sometimes gave positive delayed reactions.

which were indistinguishable from those produced by heat-inactivated virus. It was thus evident, first, that no single normal cord preparation could be regarded as a proper control, and second, that toxic substances which give delayed skin reactions may be present in certain preparations of either normal or poliomyelitic spinal cords. Whether these toxic substances are of bacterial or of autolytic origin is not clear.

In view of the foregoing facts, there is at the present time no definite evidence for the existence of cutaneous allergy to the heat-inactivated virus of poliomyelitis in human beings, although such a possibility is not conclusively eliminated. Hence there is no basis for a skin test which would differentiate between susceptibility and resistance to the disease. Whether or not unheated virus may act differently in this respect is not known and must await the results of further investigations, which are naturally fraught with certain difficulties and remote dangers.

The medical staffs of the New York State Reconstruction Home at Haverstraw, N. Y., and the Willard Parker Hospital, New York, cooperated and assisted in this work.

# EXCRETION OF NITROGEN BY OBESE PATIENTS ON DIETS LOW IN CALORIES, CONTAINING VARYING AMOUNTS OF PROTEIN

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In planning reducing diets for obese patients, the aim should be to facilitate the loss of stored fat without damaging the body structure. Older investigators<sup>1</sup> advocated high protein diets, but did not agree on the effects of such diets on nitrogen equilibrium. Mason<sup>2</sup> expressed the belief that it is unnecessary to maintain obese patients in nitrogen equilibrium, since serious losses of nitrogen do not occur. More recently<sup>3</sup> he has pointed out the strong tendency of such patients to conserve nitrogen, and he stated that patients who lose weight most rapidly also lose more nitrogen per day. Strang, McClugage and Evans<sup>4</sup> observed early small losses of nitrogen and later an equilibrium when small quantities of carbohydrates were added to low caloric diets.

Because of the rather prevalent view among clinicians that under-nutrition subjects the body to bacterial invasion and overnutrition protects against infections, it is important to study the excretion of nitrogen in the obese patient on low and on high protein diets which are below his caloric requirements. Such a study should yield information of clinical value.

## EXPERIMENTAL METHODS

*Handling the Patient*—The patients were hospitalized during the experimental period, and their meals were served from a special diet kitchen. Some were “bed patients,” others were “ambulatory.” They were weighed each morning before breakfast under standard conditions.

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From the Department of Medicine, University of Illinois College of Medicine.  
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1 Howard, C. P. Obesity, in Oxford Medicine, New York, Oxford University Press, 1921, vol. 4, p. 195. Dapper, Carl. Ueber Entfettungskuren, Arch. f. Verdauungskr. **3** 1, 1897. Hirschfeld, F. Ueber den Eiweissverlust bei Entfettungskuren, Berl. klin. Wchnschr. **31** 621, 1894.

2 Mason, E. H. Treatment of Obesity, Canad. M. A. J. **14** 1052, 1924.

3 Mason, E. H. Studies upon Obesity. Source of Heat During Periods of Reduction, J. Clin. Investigation **4** 93, 1927.

4 Strang, J. M., McClugage, H. B., and Evans, F. A. Nitrogen Balance During Dietary Correction of Obesity, Am. J. M. Sc. **181** 336, 1931.

The urine was preserved in the icebox and analyzed daily for total nitrogen (macro-Kjeldahl), creatinine (Folin<sup>5</sup>),  $p_H$  (LaMotte Comparator<sup>6</sup>) and specific gravity. The fecal nitrogen was estimated as ten per cent of the food nitrogen. Analysis of the feces was not made.

*Measuring the Energy Requirements*—It has been generally accepted that the basal requirements of the obese patient, measured in the usual way and expressed as a function of the surface area, is normal. Recently, Evans and Strang<sup>7</sup> suggested that the obese patient should be analyzed into a body machine, the size of which is expressed in the ideal body weight as determined by the age, height and sex factors, and into an extracorporeal mass of fat. This machine, with its surface area reduced by the exclusion of the fat, is the unit to which they estimate the energy should be supplied.

The agreement between metabolic rate and surface area in mammals of different sizes is so close that it seems unwise to deviate from this established principle of measuring the energy requirements. The basal rates of the subjects were observed repeatedly and found within the normal limits of persons of the same surface area, sex and age. The caloric value of the diets, therefore, is expressed as a percentage below this normal basal, as basal minus 30 per cent.

*Diets*—The values of the foods were computed from the analyses as published in Bulletin 28 of the United States Department of Agriculture<sup>8</sup>. In estimating the calories derivable from a diet, the caloric value of proteins and carbohydrates was placed at 4 and of fats at 9. The diets first used contained 90 Gm of protein and quantities of carbohydrate and fat sufficient to make up the desired calories. For convenience this is called a high protein diet. In reality it contains only an average quantity of protein. Many of the patients weighed between 100 and 150 Kg, and on this basis the protein of the diet would vary between 0.6 and 0.9 Gm per kilogram of body weight. It is difficult to estimate the energy expended by these patients in the course of the day. They were ambulatory, some quite active and others sedentary. It seems safe to assume that the ambulatory patients were using basal plus 20 per cent calories. The diets ranged between basal minus 30 per cent and basal minus 40 per cent. On such an assumption, the patients would derive from 40 to 50 per cent of their daily energy from the body.

5 Folin, O. On the Determination of Creatinine and Creatine in Urine, *J Biol Chem* **17** 469, 1914.

6 Lamotte Chemical Company, Baltimore. Hawk and Bergeim. *Practical Physiological Chemistry*, ed 8, Philadelphia, P. Blakiston's Son & Co., 1923, p 709.

7 Evans, F. A., and Strang, J. M. The Treatment of Obesity with Low Caloric Diets, *J A M A* **97** 1063 (Oct 10) 1931.

8 Atwater, W. O., and Bryant, M. S. U. S. Dept Agric, Bull 28, 1906.

The carbohydrate varied between 60 and 150 Gm as the calories increased from 1,024 to 1,600. The patients on the diets that contained less than 30 Gm of butter were given either oscodal tablets or 5 Gm of cod liver oil to supply vitamins A and D.

*Plan of the Experiment*—On entering the hospital, the patients, during a preliminary period, received diets containing their basal requirements, which included 90 Gm of protein. After one or two weeks the calories were reduced to the desired level, with 90 Gm of protein. In the earlier experiments collection periods of urine for from five to seven days were introduced at stated intervals. In the latter experiments the urine was collected daily during the entire period. The diet contained basal minus 30 per cent calories for six weeks. At the end of this time the basal requirements were refigured and a diet given which contained 13.5 Gm of protein and basal minus 30 per cent calories for a period of six weeks. This period was followed by another one of six weeks, during which the patients received 90 Gm of protein and basal minus 30 per cent calories.

#### RESULTS

*Positive Nitrogen Balance on Diets with 90 Gm of Protein*—Table 1 shows that under the conditions of the experiment, on a diet containing 90 Gm of protein, with calories from 40 to 50 per cent below the actual requirements and from 30 to 40 per cent below basal requirements, and ambulatory activity, the patients remained in positive nitrogen balance. The retention of nitrogen was definite, the majority of values were between 1 and 2 Gm per day, with higher values of 2.2 Gm (H. H.), 2.75 Gm (M. M.) and 5.05 Gm (E. H.). In the experimental periods, which are starred in the table and which followed periods of low protein feeding, the retention of nitrogen (2.29, 4.67 and 5.65 Gm daily for forty-two days) was more striking.

Mason<sup>2</sup> reported experiments on five patients whose diets contained from 23 to 49 Gm of protein, from 10 to 62.5 Gm of carbohydrate, from 4.9 to 15.4 Gm of fat and from 202 to 650 calories. All of these patients had negative nitrogen balances for the entire experimental period, but toward the close of the period one patient was in positive nitrogen balance, and the remainder were in only slight negative balances. Strang, McClugage and Evans<sup>4</sup> fed patients diets quite similar to those of Mason, and they noted an early loss of nitrogen which ceased when the carbohydrate in the diets was raised to 20 Gm. The diets used by these investigators were much lower in protein and calories than those reported in table 1.

It was of interest to note whether patients on these diets had a negative balance at any time, and to see what significance is to be attached to such periods of negative balance. In table 2 an analysis is presented of the experiments in which sporadic periods of negative

TABLE 1—*Positive Nitrogen Balance of Obese Patients*

Patient	Experi- mental Days	Weight, kg	Age	Diet		Nitrogen, Gm		Length of Period, Days	Activity
				Protein, Gm per Day	Calories per Day	Balance in Period	Balance per Day		
S C	8 41	91.8	31	14.5	B—30% 1,171	56.534	1.61	35	Ambulatory
S C	44 79	82.7	31	14.5	B—30% 1,141	23.815	0.68	35	Ambulatory (more exer- cise)
M H	1 29	120.2	39	14.51	B—30% 1,125	9.257	0.31	25	Rest in bed
M H	68 103	107.3	39	7.98	B—30% 1,002	39.873	1.14	35	Rest in bed
H K	19 61 70 77	167.6 155.0	33	20.46	B—30% 1,575	58.95	1.2	49	Sedentary
H K	1 53	116.4	35	14.1	B—30% 1,900	75.033	1.53	49	Sedentary
N P	15-57	113.8	40	14.48	B—30% 1,141	26.029	0.62	42	Ambulatory
N P*	100 141	125.0	40	14.51	B—30% 1,370	94.290	2.299	41	Ambulatory
N P	141 183	119.5	40	14.43	B—30% 1,317	0.472	0.010	42	Ambulatory
N P	190 232	113.4	40	14.48	B—30% 1,297	-0.022	-0.0005	42	Ambulatory
N P	232 274	106.8	40	14.43	B—30% 1,266	0.210	0.005	42	Ambulatory
M M	8 50	118.0	39	14.43	B—30% 1,113	36.226	0.86	42	Ambulatory
M M*	92 134	100.1	39	14.37	B—30% 1,220	196.199	4.67	42	Ambulatory
M M	175 170	94.3	39	14.45	B—30% 1,172	96.303	2.75	42	Ambulatory
L M	8 50	127.3	44	14.51	B—30% 1,360	55.086	1.31	42	Sedentary
L M*	78 120	112.2	44	14.5	B—30% 1,386	237.542	5.65	42	Sedentary
F L	15-40	121.1	41	14.35	B—30% 1,165	43.759	1.75	25	Quite active
Y B	22 43	77.4	39	14.37	B—33% 1,054	74.335	3.54	21	Rest in bed
H H	81 88	82.7	17	14.1	B—27% 1,278	15.655	2.2	7	Ambulatory
E H	73 101	88.1	33	14.1	B—30% 1,162	141.416	5.05	21	Active
E H	15 43	97.7	33	14.4	B—30% 1,201	11.035	1.95	21	Active
M F	1 8 14 21	113.0	41	14.4	B—40% 1,014	21.69	1.55	14	Ambulatory
L R	2 16 24 31	128.1	27	14.1	B—30% 1,360	6.073	0.289	21	Ambulatory
L R	35 42	124.1	27	14.4	B—43% 1,101	10.789	1.541	7	Ambulatory

\* Present period immediately preceded by diet low in protein

balance occurred In this table, the character of diet and its duration during the preliminary period are shown In the experimental period the weeks during which the balance was positive and the weeks during which it became negative are shown In the last column, the negative balance per day is expressed in grams It should be noted that in six of the eleven experiments the balance was positive at all times In the other five experiments, there was a total of eight of forty-three weeks during

TABLE 2—*Negative Nitrogen Balance of Patients in Table 1 (Basal, 30 Per Cent \* Calories, Protein, 90 Gm )*

Patient	Preliminary Period		Experimental Period												
	Type of Diet	Duration, Weeks	Calories	Positive Balance, Weeks										Negative Balance	
														Weeks	Gm a Day
S C	Basal N 14 5	1	B — 30% 1,174	1	2	3	4	6	7	8	9	10	5	0 031	
E L	Basal N 14 5	2	B — 30% 1,465	1	2	3	4								
M M	Basal N 14 3	1	B — 30% 1,313	1	2	4	6						3	1 627	
M M	B — 30% N 2 19	6	B — 30% 1,220 1,172	1	2	3	4	5	6	7	8	9	5	0 132	
L M	Basal N 14 4	1	B — 30% 1,360	1	2	3	4	5	6						
L M	B — 30% N 2 2	4	B — 30% 1,386	1	2	3	4	5	6						
N P	Basal N 14 3	2	B — 30% 1,014	1	2	3	5	6					4	0 945	
N P	B — 30% N 2 2	6	B — 30% 1,350	1	2	3	4	5	6						
M H	Uncontrolled		B — 30% 1,425 1,002	2	3	4	5	6	7	8	9	10	1	1 056	
H K	Basal N 20 46	2	B — 30% 1,575	2	3	4	7						{ 1 5 6	2 820 0 490 2 740	
H K	Basal — 20% Protein 90 (at home)	Several months	B — 30% 1,328	1	2	3	4	5	6	7					

which there was negative balance In three of the eight weeks the balance was so slight that the patient might be considered as being in equilibrium This leaves five weeks scattered irregularly throughout the total eighty-three experimental weeks during which the balance was negative, a percentage of 6 The absence of any regularity in the location of these periods and the lack of correlation between the negative balance and the loss of weight would indicate that the loss of nitrogen is not predictable and is not essential to the loss of weight It is probably related in some way to adjustments in the deposit nitrogen

*Negative Nitrogen Balance on Diets with 90 Gm of Protein*—Table 3 summarizes the records of the patients in whom negative nitrogen balances developed. A study of this table shows that there are only four experiments (E G, L D, N P and N P\*) of sufficient duration to be comparable with those summarized in table 1. One of these patients (L D) was confined to bed. Although her negative balance was small, it probably would have been larger had she been ambulatory. One patient (E G) was reasonably active (ambulatory), but not more so than many in table 1. Her negative balance (—2.76) was definite. N P had an interesting case. At the age of 36 and while on diets of basal minus 48 per cent and basal minus 42 per cent calories,

TABLE 3—*Negative Nitrogen Balance of Obese Patients (Protein, 90 Gm, Submaintenance Diets)*

Patient	Experimental Days	Weight, Kg	Age	Diet		Nitrogen Balance		Length of Period, Days	Activity
				Protein, Gm	Calories	Per Period	Per Day		
B B	6 13	114.3	35	14.4	B—31% 1,702	—11.95	—1.71	7	Ambulatory
H M	6 13	90.7	30	11.1	B—31% 1,208	—12.15	—1.74	7	Ambulatory
L T	5 12	101.3	40	11.27	B—39% 1,023	—17.84	—2.26	7	Ambulatory
L G	1 29	139.5	25	11.1	B—30% 1,400	—77.19	—2.76	28	Ambulatory
L D	49 56 71 99	88.1	52	14.1	B—30% 1,135	—2.47	—0.07	35	Rest in bed
D S	1 8	82.3	25	15.66	B—30% 1,218	—3.22	—0.40	8	Laboratory work
N P	1 8 9 73	127.7	36	11.1	B—48% 1,014	—215.70	—3.51	70	Sedentary
N P*	107 156	99.8	36	11.27	B—42% 1,023	—60.61	—1.23	49	Sedentary

\* Followed a period of low protein.

negative nitrogen balance developed. At the age of 40, when her weight was approximately the same, and while on a diet of basal minus 30 per cent calories, she remained in positive nitrogen balance, as shown in table 1. The question arises. Is this difference in balance attributable to a difference (18 and 12 per cent, respectively) in the caloric value of the diets, or to changes within the patient between the years of 36 and 40? The subjects of the first three experiments (B B, H M and L T) had been dispensary patients, and as such they lost weight remarkably well. They would not consent to a long period of hospitalization, so were admitted for two weeks. Prior to admission, they had been living on a quantitative diet and had weighed their food daily so that the transfer to the hospital involved little change in diet. During the first week they were in the hospital, the urine was discarded, and



the analytic results of the urine collected during the second week are shown in table 2

It is evident that the number of patients in whom negative balances developed while on diets of this character is much smaller than the

TABLE 4—Summary of Results on Low Protein Diets

Name	Weight, Kg	Age	Calories	Length of Time on Diet, Days	Intake of Nitro- gen, Gm	Daily Nitrogen in Urine	Daily Total Nitrogen (Urine N <sub>2</sub> + 10% N <sub>2</sub> )	Daily Nitrogen Balance,	Experi- mental Days	Activity
						Averaged for Seven Days, Gm	Intake for Seven Days, Gm	Averaged for Seven Days, Gm		
S C	82 7 to 78 4	31	B — 30% 1,144	42	2 11	3 652	3 86	—1 76	42	Ambulatory
						3 978	4 19	—2 08		
						3 846	4 06	—1 05		
						4 437	4 65	—2 53		
						3 803	4 01	—1 90		
						4 016	4 23	—2 12		
H K	154 3 to 147 7	33	B — 26% 1,574	14	2 02	7 82	8 02	—5 32	12	Sedentary
						4 17	4 37	—2 36		
	110 0 to 102 7	35	B — 29% 1,315	45	2 05	5 18	5 38	—3 32	42	Sedentary
						3 68	3 89	—1 84		
						3 47	3 67	—1 63		
						3 63	3 83	—1 78		
						2 38	2 58	—1 54		
						3 13	3 33	—1 28		
H H	83 8 to 83 9	17	B — 32% 1,201	11	2 24	5 10	5 33	—3 09	5	Ambulatory
M M	108 1 to 104 5	39	B — 30% 1,233	42	2 19	4 25	4 47	—2 28	42	Ambulatory
						2 98	3 20	—1 01		
						2 64	2 86	—0 66		
						3 68	3 897	—1 71		
						3 11	3 33	—1 14		
						4 19	4 40	—2 21		
L M	118 1 to 112 2	44	B — 30% 1,310	32	2 20	3 95	4 17	—1 97	28	Ambulatory
						2 73	2 95	—0 75		
						2 58	2 80	—0 799		
						3 20	3 42	—1 22		
N P	108 9 to 100 2	36	B — 42% 1,067	32	2 02	5 49	5 69	—3 68	31	Ambulatory
						4 51	4 71	—2 70		
						3 47	3 68	—1 66		
						4 91	5 12	—3 10		
	93 6 to 85 4	36	B — 39% 1,067	46	2 02	6 85	7 05	—5 03	45	Ambulatory
						3 91	4 12	—2 15		
						5 12	5 33	—3 31		
						4 61	4 82	—2 80		
						3 68	3 89	—1 87		
						4 19	4 40	—2 38		
	134 8 to 125 2	40	B — 30% 1,365	43	2 20	3 67	3 89	—1 69	42	Ambulatory
						3 96	4 18	—1 98		
						2 67	2 89	—0 69		
						2 95	3 17	—0 97		
						2 01	2 23	—0 03		
						1 36	1 58	+0 62		

number in whom positive balances developed This may be a characteristic reaction of these particular subjects to submaintenance diets containing an adequate quantity of protein The significance of this point will be discussed later

*Negative Balance on Low Protein Diets*—Since patients showed a marked tendency to conserve nitrogen on diets containing 90 Gm of protein, it was important to know the effect of diets low in protein (from 12.5 to 14 Gm). In table 4 the results of such studies are summarized. In column 7, the daily excretion of nitrogen, averaged over seven days throughout the experiments, is shown. Column 9 shows the daily negative balance computed in the same way. Again one is struck by the frugality of protein metabolism under this extremely low intake of nitrogen.

*Nitrogen Minimum*—Since the excretion of nitrogen was low, it was decided to compare it with the values for "wear and tear nitrogen" or "nitrogen minimum." A patient (N. P., table 5) who had been cooperative was selected for this study. A palatable diet, low in nitrogen and containing an excess of calories (basal plus 50 per cent), was used. Her requirements under the condition of hospital life could not have exceeded basal plus 30 per cent. During the first two days the diet consisted of 400 Gm of starch and 300 Gm of cream, but this was abandoned because it was unpalatable. For the next four days the diet consisted of 200 Gm of 36 per cent cream, 100 Gm of bananas, 200 Gm of lemon juice, 83 Gm of butter, 100 Gm of boiled potato, 20 Gm of dry rice and 156 Gm of dextrose. During the remaining nine days the cream in the diet was raised to 300 Gm, and the other articles remained the same. From the table (column 2) it will be noted that there were some variations in the intake of nitrogen. The earlier differences are accounted for by the changes in the character of the food at the end of the second and the sixth days. Total estimations of nitrogen were made on each new bottle of cream and some variations were found. This factor alone accounts for the differences in the intake of nitrogen during the last nine days.

Variations in fat also must have occurred in the samples of cream but these were not estimated. Since the calories were evidently in excess of the patient's requirements, such variations were not considered important. There are in this experiment the standard conditions for the determination of the nitrogen minimum. It may be noted (column 3, table 5) that after the sixth day the urinary nitrogen dropped below 3 Gm, and reached a value of 2.24 Gm on the fifteenth day. These values are close to those reported by Thomas and others<sup>9</sup> but not so low as those (1.76 Gm) obtained by Deuel, Sandiford, Sandiford and Boothby<sup>10</sup> in an experiment lasting a much longer time.

<sup>9</sup> Thomas, Karl. Ueber das physiologische Stickstoffminimum, Arch f Physiol (Supp Bd, 1910), p 249. Landgren, Ernest. Untersuchungen uber die Eiweissumsetzung der Menschen, Skandinav Arch f Physiol **14** 112, 1903.

<sup>10</sup> Deuel, H. J., Jr., Sandiford, I., Sandiford, K., and Boothby, W. M. A Study of the Nitrogen Minimum, J Biol Chem **76** 391, 1928.

In the next experiment the nitrogen in the diet was 22 Gm (estimated from bulletin 28<sup>8</sup>) and the calories were basal minus 30 per cent. The first fourteen days of this period followed a period during which the diet consisted of 90 Gm of protein and basal minus 30 per cent calories. The behavior of the nitrogen (column 4, table 5) is quite similar in the two experiments. In the fifth column, the values for the excretion of nitrogen during the fourteen days from the twenty-eighth to the forty-second day of the same experiment are shown. On these days the values reached the levels recorded by Smith<sup>11</sup> and by Deuel, Sandiford, Sandiford and Boothby<sup>10</sup> for a normal subject. It should be emphasized at this point that the caloric value

TABLE 5—*Nitrogen Excretion of Obese Patients Under Specific Nitrogen Hunger and Varying Number of Calories (Nitrogen Minimum)*

Weight	98.4 Kg	134.5 Kg	129.5 Kg	98.4 Kg
Diet	B + 50%	B — 30%	B — 30%	B — 61.5%
COH	(app.) 243.3	163.0	163.0	149.6
Nitrogen	(app.) 1.7	2.201	2.201	0
Calories	2,630	1,365	1,365	598.4
On diet	115 days	114 days	28.42 days	110 days
Days	Intake of Nitrogen, Gm	Urine Output of Nitrogen, Gm	Urine Output of Nitrogen, Gm	Urine Output of Nitrogen, Gm
1	0.723	5.90	5.62	1.48
2	0.723	3.49	5.23	0.33
3	1.528	5.10	4.37	0.97
4	1.528	4.05	3.33	3.996
5	1.528	3.25	3.42	2.13
6	1.478	3.64	1.60	2.53
7	1.725	2.89	2.13	2.62
8	1.586	2.84	3.26	1.26
9	1.586	2.40	2.70	0.93
10	1.619	2.93	1.47	1.97
11	1.619	2.83		1.66
12	1.821	3.37		1.50
13	1.821	3.05	4.94	1.17
14	1.725	2.76	3.76	1.02
15	1.573	2.24	4.54	1.53

of this diet is approximately 40 per cent below the actual energy expended by the patient.

A third experiment is shown in column 6 of table 5. In this case the patient was given 200 Gm of lemon juice and 130 Gm of dextrose, making a total of 148.6 Gm of carbohydrate and 598.4 calories per day. This diet was approximately from 67 to 70 per cent below the actual energy requirements of the patient. Although the experiment was continued for only ten days, the nitrogen values are of the same order as those noted in the other experiments. Whether by a continuation of the experiment over a period of fourteen days or more we would have arrived at lower values is not evident and is not important. It is quite evident that an obese patient may arrive at or

11 Smith, Millard. Minimum Endogenous Nitrogen Metabolism, J Biol Chem 68 15, 1926.

approximate closely the nitrogen minimum in the urine providing the intake of nitrogen is reduced to the proper level and sufficient carbohydrate is given to meet his requirements for this food. It is not necessary, as in the case of the normal subject, to supply him with an excessive caloric intake. The stored fat is readily available and meets any caloric deficit that may arise.

*Excretion of Creatinine*—The daily excretion of creatinine was not a constant quantity even on a meat-free diet. The data shown in table 6 were obtained from seven women and one man. These patients were eating diets containing basal minus 30 per cent calories, with the exception of M. H., who was on basal minus 48 per cent calories. The meat-

TABLE 6—Daily Excretion of Creatinine on Reducing Diets

N P		M M		L M		M H		S C		H K		M D†		E L
14 4	2 2	14 4	2 19	14 4	2 2	14	7 98	14 4	2 11	14 4	2 04	14 4	2 176	14 4
0 467	0 512	0 588	0 278	0 443	0 263	0 583	0 351	0 589	0 488	0 622	0 512	0 537	0 576	0 865
0 526	0 496	0 489	0 388	0 440	0 427	0 474	0 367	0 605	0 484	0 529	0 526	0 476	0 604	0 594
0 485	0 510	0 511	0 427	0 575	0 362	0 560	0 447	0 484	0 457	1 049	0 509	0 528	0 539	0 651
0 536	0 464	0 412	0 374	0 441	0 326	0 501	0 423	0 708	0 540	0 941	0 592	0 518	0 671	0 800
0 499	0 522	0 400	0 356	0 414	0 214	0 624	0 449	0 480	0 436	0 562	0 592	0 523	0 544	0 821
0 427	0 456	0 497	0 351	0 477	0 519	0 451	0 455	0 514	0 452	0 560	0 374	0 493	0 726	0 682
0 719	0 443	0 522	0 408	0 448	0 300	0 572	0 323	0 458	0 485	0 679	0 529	0 516	0 549	0 628
0 540	0 504	0 535	0 445	0 441	0 235	0 527	0 479	0 504	0 473	0 599	0 462	0 491	0 457	0 700
0 532	0 463	0 579	0 464	0 501	0 459	0 525	0 463	0 418	0 454	0 656	0 493	0 419	0 531	0 687
0 602	0 425	0 368	0 478	0 530	0 241	0 539	0 381	0 577	0 575	0 672	0 434	0 591	0 621	0 522
0 527	0 265	0 927	0 507	0 524	0 248	0 519	0 423	0 473	0 480	0 648	0 450	0 527	0 566	0 635
0 526	0 342	0 715	0 464	0 510	0 263	0 534	0 420	0 562	0 540	0 445	0 568	0 500	0 499	0 711
0 518	0 720	0 579	0 335	0 501	0 271	0 425	0 332	0 571	0 444	0 562	0 469	0 542	0 492	0 678
0 762	0 503	0 498	0 507	0 512	0 410	0 571	0 424	0 476	0 455	0 554	0 457	0 551	0 597	0 725
Mean	0 547	0 473	0 544	0 413	0 482	0 326	0 529	0 530	0 483	0 648	0 493	0 514	0 569	0 693
MD	0 063	0 065	0 096	0 064	0 039	0 078	0 040	0 062	0 0305	0 107	0 049	0 030	0 047	0 067
MD %	11 4	13 7	17 4	15 6	8 1	23 9	7 5	11 6	6 3	16 5	9 8	5 8	8 2	9 7

\* Diets were basal—30 per cent with exception of M. H., on basal—48 per cent.

† Experiment began in case M. D. immediately after institution of diet. In all other cases experiment began two weeks after institution of diet.

containing diets had nitrogen values of 7.98 and 14.4 Gm. The meat-free diets had values of 2.1 and 2.2 Gm. of nitrogen.

The values of the excretion of creatinine are given for fourteen days. The mean (M), mean deviation (MD) and mean deviation expressed in percentage (MD %) appear at the bottom of the table. These periods of fourteen days (except patient M. D., protein, 14.4 Gm.) began between the fourteenth and twenty-first day after the patient had begun the indicated diet. It was hoped in this way to avoid any confusion that might arise from variations in the "deposit nitrogen." It may be assumed that the creatine of the meat varied between 0.3 and 0.5 Gm. (Andrew Hunter<sup>12</sup>), which, according to Benedict and Osterberg,<sup>13</sup> would yield a maximum creatinine of from 0.09 to 0.15

12 Hunter, Andrew. Creatine and Creatinine, Monograph on Bio-Chemistry, New York, Longmans, Green & Co., 1928, p. 114.

13 Benedict, S. R., and Osterberg, E. Studies in Creatine and Creatinine Metabolism, J. Biol. Chem. 56: 229, 1923.

Gm if all of the creatine eaten were retained within the body. If only 60 per cent were retained, as their figures would indicate, then the creatinine derived from this source would vary between 0.054 and 0.09 Gm.

From an examination of the means it will be noted that the excretion of creatinine was somewhat higher on the meat-containing diet. The case of M. D. forms an exception to this rule. However, the fourteen days (being the only ones available) selected for this study were the first fourteen days immediately following the institution of the diet containing 14.4 Gm of nitrogen, and for this reason they are not strictly comparable.

The differences in the excretion of creatinine on creatine-free diets (low protein) and creatine-containing diets may be due not only to the actual amount of creatine in the diet, but also to the prolonged use of a low protein, creatine-free diet, which Ringer and Raiziss<sup>14</sup> have previously reported as causing a lowering of the excretion of creatinine.

Reference to the mean deviations expressed in percentages will show that the daily variations may be considerable. In five of fifteen experiments, the mean deviation was above 12 per cent, and in the other ten below 12 per cent. If the volume of urine and the total nitrogen are examined on the days on which there were large variations in creatinine, they will be found to vary independently, indicating that there were periods of retention of creatinine followed by periods of increased excretion. These findings in obese patients agree with those reported for normal subjects by McLaughlin and Blunt<sup>15</sup> and by others.<sup>12</sup>

*Excretion as Affected by Loss of Weight*—Table 7 summarizes the data on excretion of creatinine during the experimental period. Losses in body weight varying between 66.9 and 68 Kg are recorded. The mean deviation, expressed in percentage, shows that no significant changes in creatinine occurred as the result of loss in body weight. This is in keeping with the findings of McClugage, Booth and Evans.<sup>16</sup>

#### COMMENT

The excretion of nitrogen of the obese person differs strikingly from that of the normal subject. The majority of obese persons remain in positive balance when from 50 to 90 Gm of protein is fed.

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14 Ringer, A. L., and Raiziss, G. W. Excretion of Creatinine by Human Individuals on a Prolonged Creatinine Free Diet, *J Biol Chem* **19** 487, 1914.

15 McLaughlin, L., and Blunt, K. Some Observations on Creatinine Excretions of Women, *J Biol Chem* **58** 285, 1923.

16 McClugage, H. B., Booth, G., and Evans, F. A. Creatinine Excretion in Abnormal States of Nutrition, *Am J M Sc* **181** 349, 1931.

even though the diet is insufficient in calories. Even on diets containing minimal quantities of nitrogen, the loss in nitrogen is small. The normal subject (Benedict and his co-workers<sup>17</sup>) loses nitrogen under such conditions. It is further shown that the obese patient may excrete a nitrogen minimum when the calories in his food are 40 per cent below his actual requirements. These findings indicate that the stored fat is mobile and easily shifted into the metabolizing mixture when the food is deficient in calories. Briefly, it is impossible to induce in obese persons the sequelae of undernutrition found in the normal subject provided protein and carbohydrate are fed in quantities sufficient for antiketogenesis and for meeting the "wear and tear quota" of nitrogen. The store of fat protects the body's nitrogen against demands for energy.

In the group of persons who lost nitrogen on these diets, the subjects were of the same weight and appearance as their associates. There may

TABLE 7—*Excretion of Creatinine as Effected by Loss of Weight*

Patient	Duration of Experiment		Loss of Weight, Kg	Creatinine Excretion		
	Weeks	Number of Analytic Weeks		Mean, Mg of Nitrogen	Mean Deviation, Mg of Nitrogen	Mean Deviation, per Cent
H K (1928)	14	14	23.2	0.530	0.040	7.6
H K (1930)	16	16	14.1	0.543	0.064	11.8
H K (1928-1930)	104	30	66.9	0.537	0.034	10.0
N P	56	56	56.8	0.515	0.041	7.96
L M	18	18	21.3	0.478	0.087	18.2
M M	26	26	28.9	0.498	0.079	11.8
S C	18	18	13.1	0.500	0.048	9.6
M H	15	15	16.6	0.520	0.051	9.8
M D	9	9	6.8	0.558	0.039	10.5

have been a greater expenditure of energy by these subjects than by their obese associates, although they were living under the same conditions, and thus the mobilization of fat may not have been sufficiently rapid to protect the nitrogen. On the other hand, the obesity defect in these persons may have been less severe, and it may be that in this respect they resembled more closely the normal person. If this is true, then this preservation of a positive nitrogen balance while eating a diet markedly deficient in calories would become a characteristic finding of persons with the obesity defect, and its appearance would have diagnostic significance.

#### CONCLUSIONS

1. A majority of the obese patients studied maintained a positive nitrogen balance when fed 90 Gm. of protein per day and a diet from 40 to 50 per cent below their energy requirements.

<sup>17</sup> Benedict, F. G., Miles, W. R., Roth, P., and Smith, H. M. *Human Vitality and Efficiency Under Prolonged Restricted Diet*, Washington, D. C., Carnegie Institution, 1919, publication no. 280.

2 In a smaller number a negative balance developed under similar conditions

3 When the obese patient is fed from 13 to 14 Gm of protein per day, the negative nitrogen balance is small

4 It was shown in one case that the nitrogen minimum obtained on a diet containing 1,365 calories (which was 46 per cent below the actual requirements) was smaller than one obtained on 2,630 calories (which was 15 per cent above the actual requirements)

5 The fat constitutes a mobile supply of energy which is so easily requisitioned that starvation sequelae do not develop in the obese patient provided carbohydrate is furnished for antiketogenesis and protein for the "wear and tear quota"

6 The daily excretion of creatinine is reasonably constant, but periods of retention are succeeded by periods of increased excretion. The mean deviation calculated over periods of fourteen days often shows a variation exceeding 10 per cent

7 The weekly variations are quite constant, and the mean deviation calculated over the period of loss of weight did not show more than a 10 per cent variation, when this loss amounted to 56.8 and 66.9 Kg, respectively. It is evident that excretion of creatinine is not affected by the loss of weight produced in this manner

8 It was suggested that the patients in whom a negative nitrogen balance developed had a less severe obesity defect

# HISTAMINE TEST MEALS

## AN ANALYSIS OF NINE HUNDRED AND EIGHTY-EIGHT CONSECUTIVE TESTS

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SAN FRANCISCO

During the past few years the growing emphasis on quantitative and biometric methods in clinical medicine has brought into question the older methods of studying gastric secretion, and numerous articles have appeared in which the attempt is made to reassess the various forms of test meal. For reasons previously exposed,<sup>1</sup> histamine seems the best available agent for the clinical study of gastric secretion, and the histamine test has been systematically used in this clinic for the past four years. The records of 988 tests are now available, a number that is large enough to yield conclusions more or less definitive. The present article deals with an analysis of this material.

### MATERIAL

The subjects included patients with gastro-intestinal complaints, and also a large group who were subjected to the test as part of a general diagnostic study. There were a good many persons to all intents and purposes normal (table 1). The miscellaneous group includes cases of cardiovascular disease, tuberculosis, pernicious anemia, diseases of the liver and gallbladder, infestations with parasites and other diseases. There were not enough of each to justify separate analysis. The excess of male subjects is mainly due to the preponderance of this sex in the hospital clientele.

Table 2 shows the distribution by age periods. Most of the patients were between the ages of 20 and 69, and outside of this range the material is inadequate.

### METHODS

The test procedure has been amply described in previous papers.<sup>2</sup> Briefly, the subject fasts for at least twelve hours and is examined in the basal state. A Wilkins tube is introduced into the stomach, and after withdrawal of the fasting contents 0.1 mg. of histamine (beta-iminazolyethylamine hydrochloride) per ten

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1 Bloomfield, A. L., and Polland, W. S. The Diagnostic Value of Studies of Gastric Secretion, *J. A. M. A.* **92** 1508 (May 4) 1929

2 Polland, W. S., Roberts, A. M., and Bloomfield, A. L. The Chloride, Base and Nitrogen Content of Gastric Juice After Histamine Stimulation, *J. Clin. Investigation* **5** 611, 1928. Bloomfield and Polland<sup>1</sup>



kilograms of body weight is injected hypodermically. The total secretions are then aspirated over successive ten minute periods until the flow of juice subsides (about one hour). The greatest volume of juice secreted in a ten minute period and the highest titratable acidity attained are taken as indexes of the secretory capability of the stomach and furnish the data on which this report is based. Two hundred and thirty-five of the examinations were performed by me, the others were made by members of the house staff or by specially trained technicians.

In a large series of cases the average difference between free and total acidity was found to be 10 cc of tenth-normal hydrochloric acid per hundred cubic centimeters of gastric juice, in order to avoid duplication, therefore, only the total acidity is tabulated. Furthermore, by using total acidity it is not necessary to group all cases of "anacidity" on the zero abscissa.

TABLE 1—*Classification of Material*

	Males	Females	Total
Normal persons	384	270	654
(Unexplained anacidity)	41	38	79
Duodenal ulcer	112	18	130
Gastric ulcer	31	5	36
Carcinoma of stomach	46	10	56
Miscellaneous	43	69	112
Total	616	372	988

TABLE 2—*Relation of Age to Material Studied*

Age	Males	Females	Total
10 19	8	6	14
20 29	107	56	163
30 39	124	93	217
40 49	166	85	251
50 59	118	78	196
60 69	68	39	107
70 79	23	14	37
80 89	2	1	3
Total	616	372	988

## NORMAL STANDARDS

Interpretation of findings in disease is obviously impossible except by comparison with sound normal standards. Pollard and Bloomfield,<sup>3</sup> recognizing this need in the present connection, made a careful analysis of the results of histamine tests in 100 normal people. While the series was small, the wide range of acid and of volume was emphasized, as well as the tendency for the rate of secretion to fall with advancing years, a point already touched on by Bloomfield and Keefer.<sup>4</sup> No attempt was made to analyze separately the findings in the two sexes until the appearance of the comprehensive report of Vanzant and

3 Pollard, W. S., and Bloomfield, A. L. Normal Standards of Gastric Function, *J. Clin. Investigation* 9: 651, 1931.

4 Bloomfield, A. L., and Keefer, C. S. Gastric Acidity: Relation to Various Factors Such as Age and Physical Fitness, *J. Clin. Investigation* 5: 285, 1928.

Alvarez and their associates<sup>5</sup> In a study of 3,746 test meals (Ewald and Ewald plus histamine), they, too, found a decline of acidity in males as age increased, but there was practically no change in the females. Volume of secretion was not considered.

The group selected as "normal" for the present study included people who had no evidences of any significant disease, who were free from digestive symptoms and who on physical and laboratory examination showed no signs of disease of the gastro-intestinal tract. Patients with acute febrile conditions, with cachexia or with any disorder that presumably might derange gastric function, such as cardiac decompensation, were excluded. Patients with unexplained anacidity, however, provided they met the foregoing specifications in other ways, were accepted.

*Acidity*—In table 3, the distribution by age of the highest total acidity in both sexes (normal) is shown. The most striking finding is the wide variation of acidity at all age periods, which makes it evident that no narrow standards of normality can be set up. The total range in both sexes is from 0 to 160 units of acid. On calculating the coefficient of correlation between age and gastric acidity, the results were found to be  $-0.236 \pm 0.033$  for the male subjects, a value which is significant and indicates a slight negative correlation between age and acidity, and  $-0.146 \pm 0.041$  for the female subjects, a value which is hardly significant. A comparison of the mean values for each age period shows that in the male subjects there is a definite decrease in acid with advancing years, but hardly any falling off in the older female subjects. A comparison of the two sexes also shows that the female subjects have in each decade a much lower acidity, except in the higher age group, in which the values for the male subjects decrease to the female level. These two important points have recently been emphasized by Vanzant<sup>5</sup>. Chart 1 shows graphically the mean total acidity in various decades.

Even if the cases of anacidity are excluded, the average total acidity falls with age in the male subjects, but it remains practically constant in the female subjects.

*Volume*—In table 4, the distribution by age of the volume of secretion is shown. Here, also, there is considerable variation, but the coefficient of correlation between age and volume for the male subjects is  $-0.331 \pm 0.031$ , and for the female subjects,  $-0.276 \pm 0.038$ , values which are significant. It is apparent that the female subjects have a mean volume of secretion less than the male subjects for all

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<sup>5</sup> Vanzant, F. R., Alvarez, W. C., Eusterman, G. B., Dunn, H. L., and Berkson, Joseph. The Normal Range of Gastric Acidity from Youth to Old Age, Arch Int Med **49**:345 (March) 1932.

age periods, and that the secretory volume decreases appreciably from youth to old age Chart 2 shows graphically the mean volume both with and without the cases of anacidity

TABLE 3—Total Acidity in Relation to Age and Sex (Normal Persons)

Units of Acid	Males								
	Age, Years								
	10 19	20 29	30 39	40 49	50 59	60 69	70 79	80 89	Total
150 159		1		1	2				4
140 149	1	10	5	1	3	1			21
130 139	1	11	7	10	3				32
120 129		7	12	14	6	5		1	45
110 119	2	6	4	13	5	3	4		37
100 109		5	10	11	6	2			34
90 99	3	7	10	10	6	2			38
80 89		6	7	6	2	2			23
70 79		4	7	7	5	1	1		25
60 69		4	9	6	8	3			30
50 59		4	4	6	1	4	1		20
40 49		1	5	5	4	1			16
30 39			2	1	3		1		7
20 29		1	1	5	2		3		12
10 19		2	2	7	6	9	1		27
0 9		1	1	4	3	2	1	1	13
Total	7	70	86	107	65	35	12	2	384
Mean		101.1	91.5	86.0	80.0	67.1			
Probable error of mean		2.86	1.83	2.54	3.56	4.98			
Standard deviation		35.7	25.2	38.8	42.6	43.7			
Coefficient of variability		35.3	27.5	45.1	53.3	43.7			
Mean of 326 cases with free acid		105.9	94.4	95.2	91.1	92.0			

Units of Acid	Females								
	Age, Years								
	10 19	20 29	30 39	40 49	50 59	60 69	70 79	80 89	Total
150 159			1						1
140 149		1		1					2
130 139		2	3		1	2			8
120 129			8	3	3	1	1		16
110 119		6	3	4	1	2	1		17
100 109		3	5	7	6	4			25
90 99	1	9	3	9	8	4	1		35
80 89	1	1	9	7	4	2			24
70 79		5	8	10	4				27
60 69		6	3	3	2	3	1		18
50 59	1	3	7	3	2	3			19
40 49		4	5	3	4			1	17
30 39		2	3	2	2	4			13
20 29			4	4	3				11
10 19		1	3	7	2	2	1		16
0 9			2	5	8	5	1		21
Total	3	43	67	68	50	32	6	1	270
Mean		82.2	76.3	68.8	65.3	66.7			
Probable error of mean		3.17	3.04	3.04	3.79	5.16			
Standard deviation		29.6	36.9	37.2	39.8	41.8			
Coefficient of variability		36.0	48.4	54.1	60.9	62.7			
Mean of 224 cases with free acid		85.5	82.1	73.2	78.7	83.0			

In order to determine whether there is a true decline of gastric function with advancing years, it is necessary to know the total amount of acid secreted in each age period This value is obtained by multiplying the mean volume by the mean total acidity for each decade If,

then, the value in the age period from 20 to 29 is taken as 100 per cent it is possible to estimate the percentage decline of gastric secretion in other age periods This is shown in chart 3, and it is seen that there

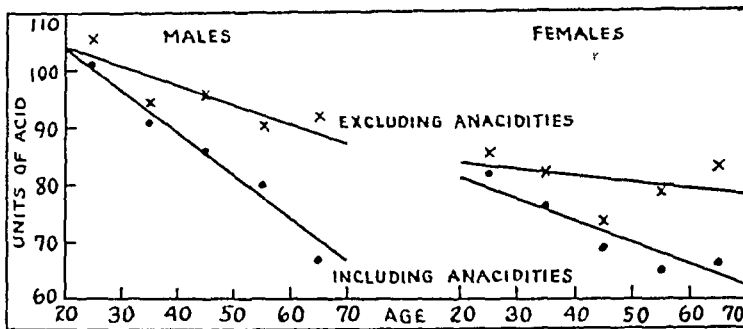


Chart 1—Standards of normal Relation of total acidity to age in various decades

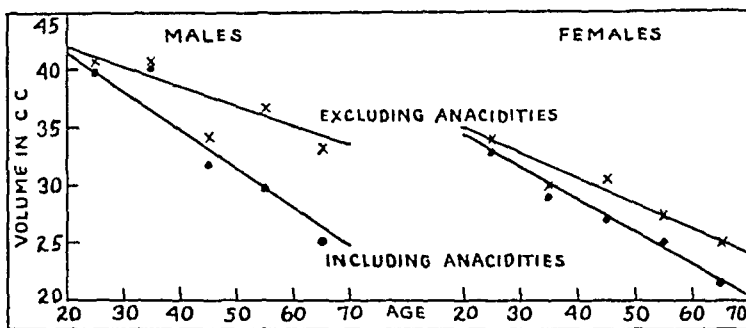


Chart 2—Standards of normal Relation of volume to age in various decades

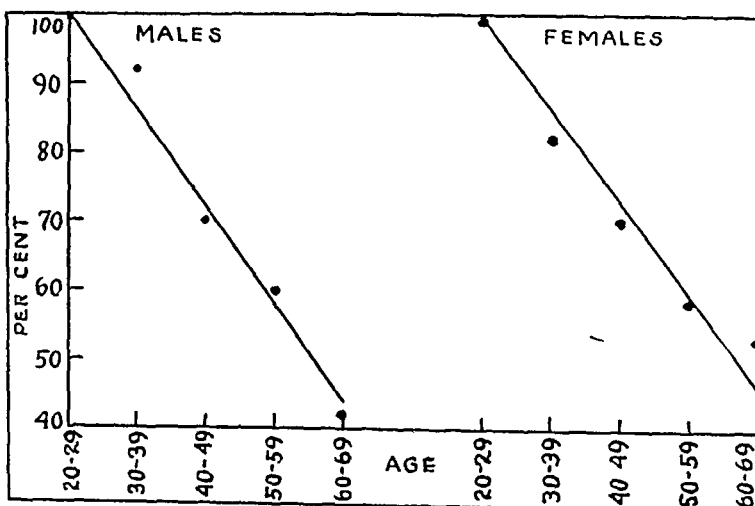


Chart 3—Percentage decrease in total gastric secretion (volume times acidity) with advancing years (normal persons)

is a similar decrease in the total amount of secretion in both sexes The importance of measuring the volume of secretion is clearly brought out, because if acidity alone is considered, it would appear that secretion decreased with age only in male subjects

TABLE 4—*Volumes of Secretion in Relation to Age and Sex (Normal Persons)*

Volume, Cc	Males								
	Age, Years								
	10 19	20 29	30 39	40 49	50 59	60 69	70 79	80 89	Total
90 94		1							1
85-89									
80 84									
75 79		1	2	1	2				6
70 74	1	1	2	2					6
65-69	1		4	1					6
60 64		5	5	2	3				15
55-59			3	1	2				6
50 54		7	7	8		4			20
45 49		4	3	8	5	3			23
40 44		19	17	8	8	3			55
35-39	3	6	5	11	2	2	1	1	31
30 34		9	15	20	4	3	1		52
25-29	1	8	12	15	6	1	2		45
20 24	1	5	2	10	11	3	2		34
15-19		2	2	7	7	3	2		23
10 14			4	5	6	4	3		22
5 9		1	3	6	5	3			18
0 4		1		2	4	6	1	1	15
Total	7	70	86	107	65	35	12	2	384
Mean		39.7	40.6	32.7	29.9	24.9			
Probable error of mean		1.21	1.21	1.01	1.51	1.99			
Standard deviation		15.1	16.7	15.6	18.0	17.5			
Coefficient of variability		38.0	41.1	45.8	60.0	70.0			
Mean of 326 cases with free acid		40.7	40.7	34.2	36.8	33.2			

Volume, Cc	Females								
	Age, Years								
	10 19	20 29	30 39	40 49	50 59	60 69	70-79	80 89	Total
90 94									
85 89									
80 84									
75 79			1						1
70 74			1						1
65 69									
60 64		3		2	1				6
55 59	1				1				2
50 54	1	1	2	2	3	1			10
45 49		4	3	4	1				12
40 44		3	5	5	1	2			16
35 39	1	7	7	3	2	1	1		22
30 34		7	14	10	9	6			46
25 29		6	4	9	6	3	2		30
20 24		5	16	9	7	4			41
15 19		6	6	6	6	2	1		27
10 14		1	4	4	6	8	1	1	25
5 9			4	11	5	4			24
0 4				3	2	1	1		7
Total	3	43	67	68	50	32	6	1	270
Mean		33.1	29.1	27.4	25.1	21.7			
Probable error of mean		1.29	1.11	0.97	1.36	1.45			
Standard deviation		12.6	13.5	11.8	14.3	12.2			
Coefficient of variability		38.1	40.4	43.1	57.0	56.2			
Mean of 224 cases with free acid		34.0	30.0	30.5	27.6	25.4			

## UNEXPLAINED ANACIDITY

With the introduction of histamine as a stimulus of gastric secretion, it has become necessary to revise preexisting ideas about gastric anacidity. Many people who apparently secrete no free acid with other stimuli, give a normal, or nearly normal, response with histamine, and it is evident that the ordinary test meal is not adequate for determining whether or not the stomach is capable of secreting acid.

It is generally agreed that the incidence of anacidity increases with age. The best study of this problem has been made by Vanzant,<sup>5</sup> and further references to the literature are given in her paper. She studied cases in which free acid did not appear on repeated fractional analysis with the Ewald meal or (in a few cases) after the injection of histamine, and found that from youth to old age there was a straight line correlation between the incidence of anacidity and age, and that at all ages women showed a greater incidence of anacidity than did men. Recently Bockus, Bank and Willard,<sup>6</sup> using the histamine method, found the general incidence of anacidity much lower in a group of patients with gastro-intestinal complaints than in normal patients. Otherwise, their findings were in agreement with Vanzant's.

In the present series of 988 cases, there were 91 instances of unexplained anacidity, 9.3 per cent. The frequency in the male subjects was 7.3 per cent, and in the female subjects, 12.4 per cent. Exclusive of cases of carcinoma of the stomach and of pernicious anemia, there was an incidence of 10.8 per cent, 8.8 per cent for the male subjects and 13.3 per cent for the female subjects.

Of the 91 cases of anacidity, 12 showed evidence of a coexisting gastro-intestinal or debilitating disease, which, on the basis of the criteria laid down for normal people, necessitated their elimination from this study. There remained, then, 79 people who, except for the absence of acid, were entirely normal. Repeated checks with histamine in many of these cases showed that the condition was constant, and I have never seen an instance of anacidity after the administration of histamine in which there was a later return of free acid.

Table 5 shows frequency of anacidity among normal people at all ages. The figures are in close agreement with those of Vanzant,<sup>5</sup> and they show that there is a definite increase as people grow older, and that at all age periods, except beyond 60, there is a higher incidence in women than in men.

## PEPTIC ULCER

The general implication of the literature is to the effect that there are no constant or characteristic findings on gastric analysis in cases

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<sup>6</sup> Bockus, H. L., Bank, J., and Willard, J. H. Achlorhydria with a Review of 210 Cases in Patients with Gastrointestinal Complaints, *Am J M Sc* **184** 185, 1932.

of peptic ulcer. However, Hurst<sup>7</sup> was impressed by the occurrence of duodenal ulcer in people who already had "hyperacidity," and while, in 53 cases of gastric ulcer, he found<sup>8</sup> 58.4 per cent with "hyperacidity," 32.1 per cent with "normal acidity" and only 9.5 per cent with "hypoacidity," no less than 90 per cent of 114 patients with duodenal ulcer had "hyperacidity" and 10 per cent had normal acidity. Brown<sup>9</sup> has summarized the question as follows: "Somewhat less than 50 per cent of patients show high normal or hyperacid conditions. Rather more than 50 per cent of cases are well within normal limits, occasionally subacidity occurs, and rarely anacidity." Cheney and Bloomfield,<sup>10</sup> using a special alcohol test meal, observed that in all but 1 of 37 cases of peptic ulcer the gastric acidity and volumes of secretion were greater than normal. Comfort and Osterberg,<sup>11</sup> using the histamine test in 40 cases of duodenal ulcer, found a range of from 30 to 135 units of acid, and in 11 cases of gastric ulcer, a range of from 25 to 95 units of acid.

Table 5 shows frequency of anacidity among the normal people at all

Age Years	Males			Females		
	Total Cases	Anacidity Cases	Percentage	Total Cases	Anacidity Cases	Percentage
10-19	7	0	0.0	3	0	0.0
20-29	70	2	2.9	43	2	4.7
30-39	86	3	3.5	67	5	7.5
40-49	107	12	10.0	68	13	19.1
50-59	65	9	13.9	50	9	18.0
60-69	35	11	31.7	32	7	21.9
70+	14	4	28.6	7	2	28.6
Total	384	41	10.7	270	38	14.1

They stated that the volumes in these cases were too variable to be of significance, but their technic is open to criticism.

In the present series there were 130 cases of duodenal ulcer, 112 in male and 18 in female patients, and 36 cases of gastric ulcer, 31 in male and 5 in female patients. In order to avoid questionable cases, the diagnosis was based on unequivocal roentgen evidence. In some instances there was surgical confirmation.

*Acidity*—The heavy line in chart 4 shows the mean total acidity at various age periods in normal people. Each dot indicates the highest total

7 Hurst, A. F. Hypersthenic Gastric Diathesis and the Pathology, Prophylaxis and Treatment of Duodenal Ulcer, *Lancet* **2** 1369, 1922.

8 Hurst, A. F., and Venables, J. F. The True Incidence of Hyperchlorhydria in Gastric and Duodenal Ulcer, *Guy's Hosp. Rep.* **9** 249, 1929.

9 Brown, T. R., in Cecil, R. L., and Kennedy, Foster. *A Text-Book of Medicine*, Philadelphia, W. B. Saunders Company, 1927, p. 655.

10 Cheney, G., and Bloomfield, A. L. Gastric Function in Cases of Gastric and Duodenal Ulcer, *J. Clin. Investigation* **5** 511, 1928.

11 Comfort, M. W., and Osterberg, A. E. Gastric Secretion After Stimulation with Histamine, *J. A. M. A.* **97** 1141 (Oct. 17) 1931.

acidity in a single case of gastric ulcer and each  $\times$  represents a single case of duodenal ulcer

That the acidity in practically every instance is above the mean is strikingly shown. There is 1 case of gastric ulcer among the male subjects in which it is below 50, and 1 case of duodenal ulcer among the female subjects in which it is below 60. Ninety-one and three-tenths per cent of all the cases of duodenal ulcer and 91.7 per cent of all the cases of gastric ulcer are above the mean line. The broken line shows the mean acidity of all the cases of ulcer. It is apparent, as in normal people,

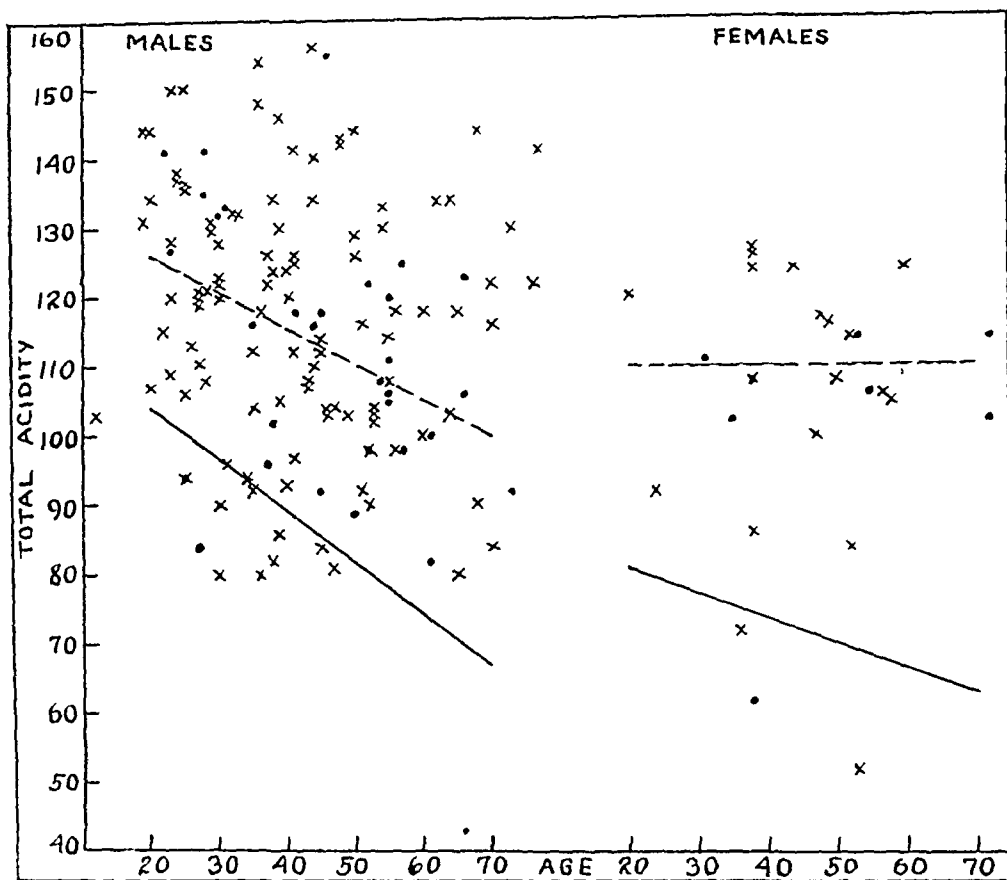


Chart 4—Total acidity in peptic ulcer Relation to normal mean

that the mean acidity of the cases of ulcer in male patients falls with advancing years. The number of female subjects is too small to be significant, but the mean acidity was about the same at all age periods.

*Volume*—In chart 5, each dot represents the maximum ten-minute volume of secretion in a single case of gastric ulcer, and each  $\times$  represents the volume in a case of duodenal ulcer. Again, one sees that the majority of cases are above the mean line. However, there is more scattering than with the acid values, and the highest volumes are in the duodenal ulcer group. There were only 8 patients in whom the volume was as low as 20 cc or less, 79.2 per cent of the cases of duodenal ulcer and 75 per cent of the cases of gastric ulcer are above the mean.



line The broken line represents the mean value for the cases of ulcer in male patients, and shows a definite fall with advancing years The mean value for the female patients could not be estimated, because there were too few cases

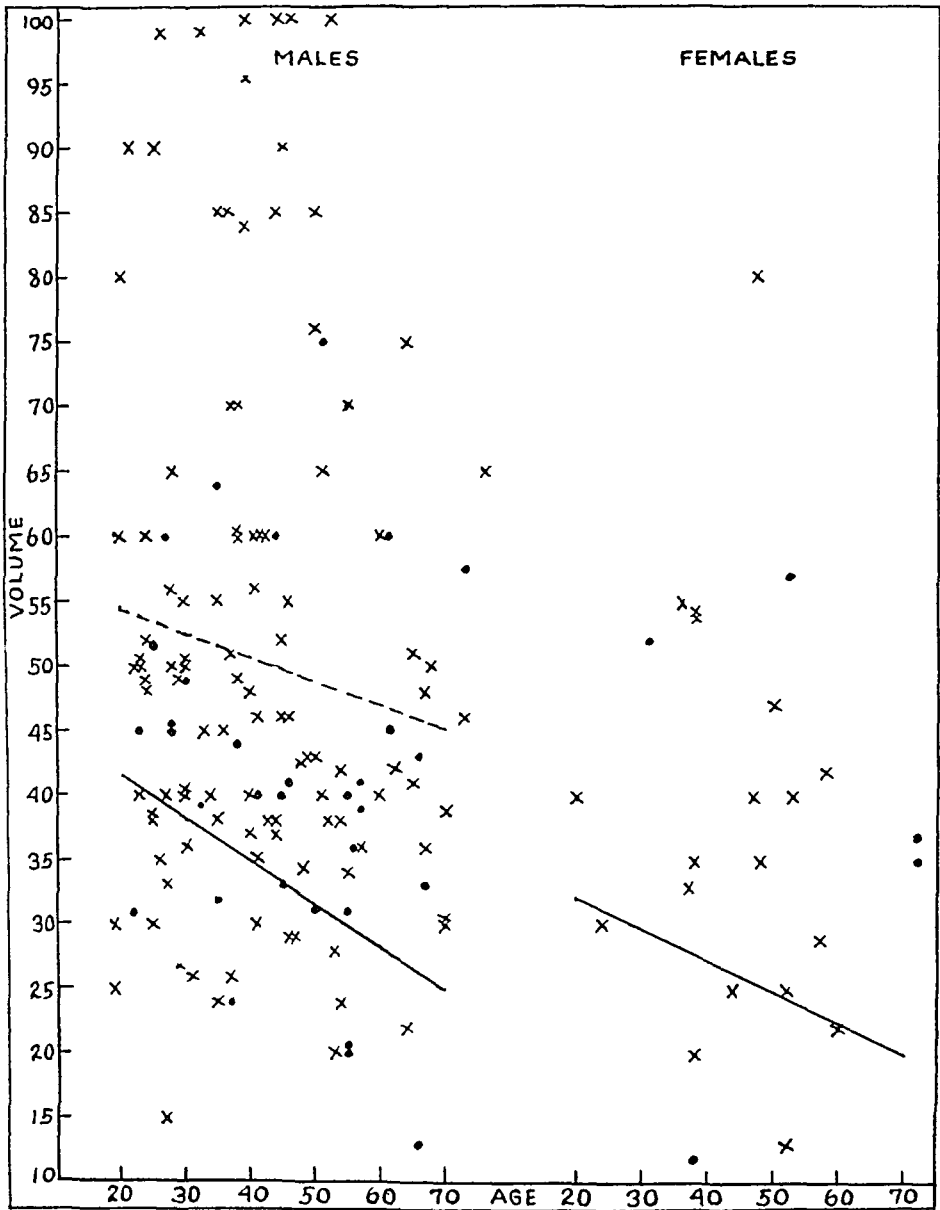


Chart 5—Volume of secretion in peptic ulcer Relation to normal mean

#### CARCINOMA OF STOMACH

One cannot here discuss the voluminous literature on gastric secretion in carcinoma of the stomach, and the reader is referred to the paper of Polland and Bloomfield<sup>12</sup> However, most observers agree

<sup>12</sup> Polland, W S, and Bloomfield, A L Gastric Secretion in Cancer of the Stomach, Bull Johns Hopkins Hosp 46 307, 1930

as to the frequency of anacidity in this disease, although they find acid present—usually diminished—in a certain percentage of cases. Practically all the reported work has been done with gastric contents removed after a test meal of some sort. High acid values have been found by very few workers in verified instances of carcinoma. The only data available on the important question of volume of secretion and on acid values after a powerful stimulus such as histamine are those of Pollard and Bloomfield,<sup>12</sup> who found, in 19 carefully studied cases, that there were usually small volumes of secretion with low acidity, or with an absence of acid.

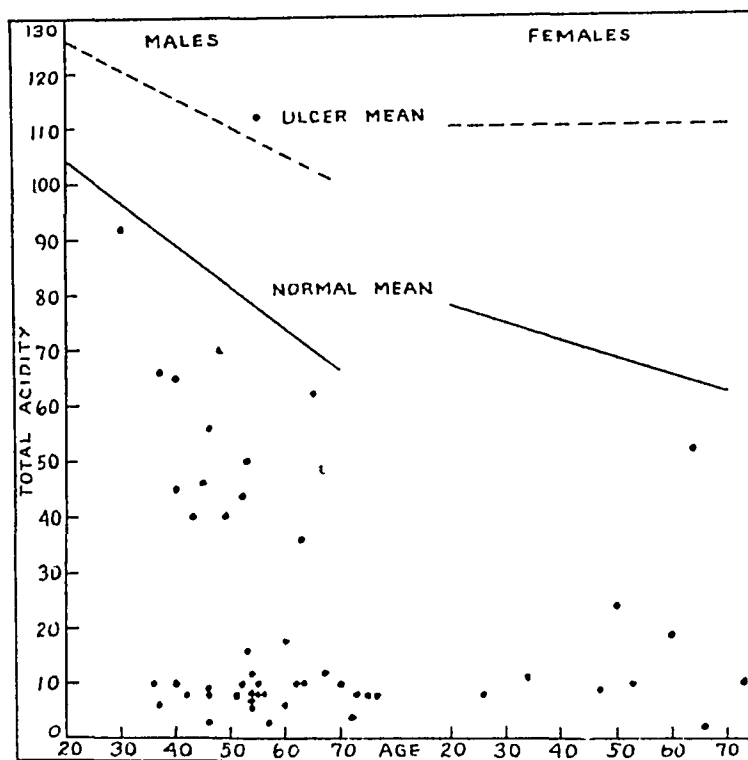


Chart 6—Total acidity in carcinoma of stomach. Relation to normal mean and to ulcer mean.

In the present series, there were 56 cases of carcinoma of the stomach, 46 in male and 10 in female patients. The diagnosis in nearly every case was verified by operation or at autopsy.

The only variation from the usual technic was that if pyloric obstruction existed, the stomach was carefully washed out before the analysis was made. This was done to avoid dealing with a mixture of foreign materials, which gives no idea of what sort of gastric juice, if any, the stomach is actually secreting.

*Acidity*—In striking contrast to the ulcer group, the majority of these patients had no acid or a low acid value. The incidence of anacidity was 69.6 per cent. In chart 6 it is seen that only 7 of the cases yielded values approaching normal, and of these, there was only 1 above

normal In this chart, the ulcer mean, as well as the normal, is given, and the relation between the type of secretion in cancer and in ulcer cases is brought out more strikingly

*Volume*—One of the most striking features of the gastric secretion in these cases is the small volume In the patients with anacidity, the maximum amount obtained was seldom over 10 cc, and the material was mostly mucus In the cases in which acid was obtained, the amount of juice was usually small In chart 7, the highest ten minute yield from all patients with carcinoma of the stomach is plotted in relation to the mean normal and mean ulcer values at various age periods

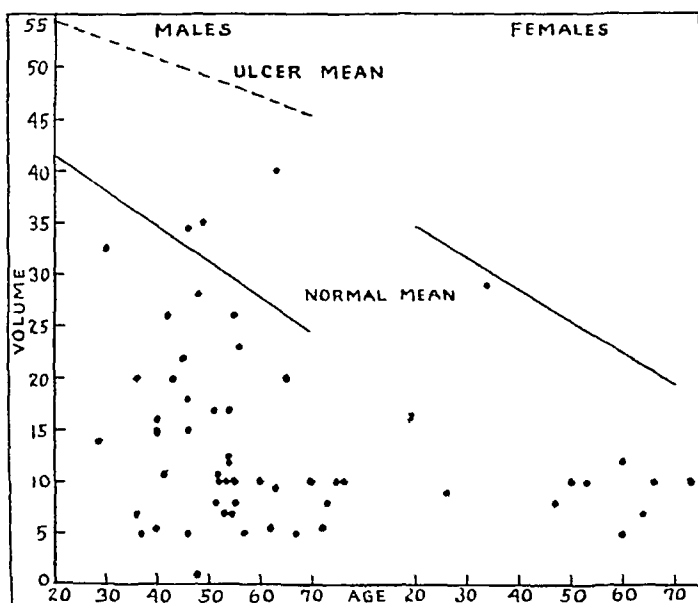


Chart 7—Volume of secretion in carcinoma of stomach Relation to normal mean and to ulcer mean

From this it can be seen that only 9 cases approach the normal, and of these, only 3 are above normal

#### DIAGNOSTIC VALUE OF HISTAMINE TEST MEAL IN DIFFERENTIATING BENIGN FROM MALIGNANT CONDITIONS OF STOMACH

One of the main objects of this study was to set standards by which findings in gastric disorders could properly be compared Are there, for example, in cancer or in ulcer, secretory findings which deviate in such a way that practical conclusions can be drawn? A glance at tables 3 and 4 (normal persons) shows that no exclusive findings are likely to be obtained in disease, and the matter resolves itself into a question of frequencies A study of charts 4, 5, 6 and 7 shows that benign and malignant diseases of the stomach yield entirely different types of gastric response to histamine Although there is some overlapping of the

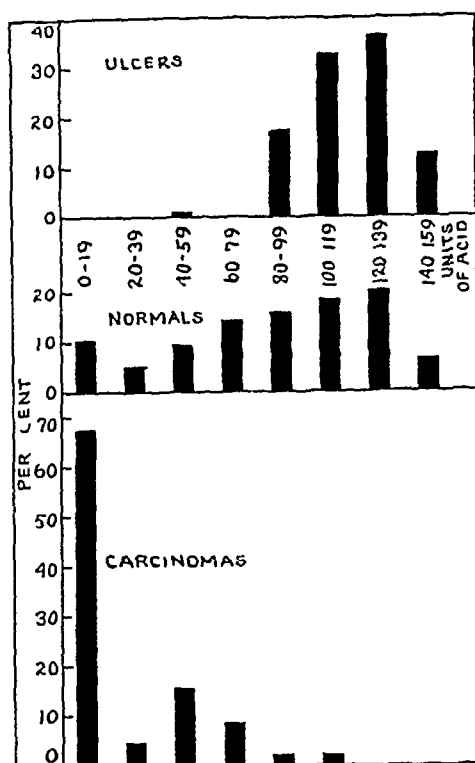


Chart 8—Frequency distribution of total acidity in normal males and in cases of carcinoma and of ulcer

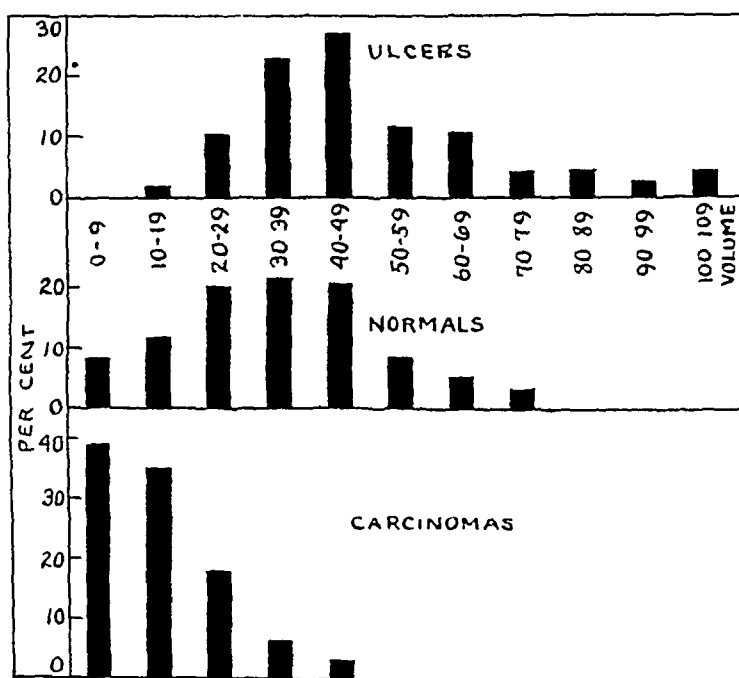


Chart 9—Frequency distribution of volume in normal males and in cases of carcinoma and of ulcer

values, particularly the volumes, the vast majority of patients with ulcer fall within the high acid, high volume range, whereas the vast majority of cases of carcinoma fall within the low acid, low volume range. To emphasize this point further, a frequency distribution of the values of total acidity in normal people and in the ulcer and cancer cases (male subjects) is shown in chart 8, and a similar graph of the volumes

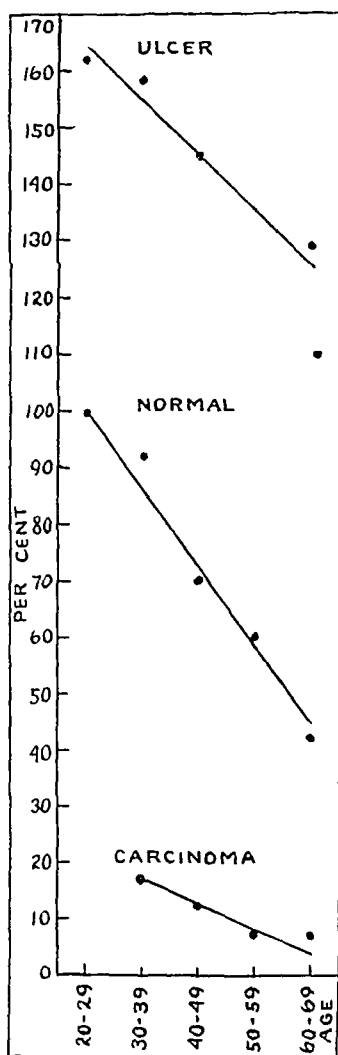


Chart 10—Percentage of total gastric secretion with ulcer and with carcinoma (males)

appears in chart 9. Although one cannot say, from the secretion, with absolute certainty that a particular lesion is benign or malignant, it seems that the original assumption of Bloomfield and Pollard<sup>1</sup> is correct, and that the histamine test meal, as advocated by them, may be of great value as a diagnostic procedure in doubtful cases of pyloric lesion.

In order to emphasize further the value of knowing the total gastric secretion (volume acid) rather than just the concentration of acid alone,

chart 10 has been constructed so that the mean total amount and acid secreted at each age period in the cases of ulcer and of carcinoma in male patients can be compared. The value in the age period from 20 to 29 of the normal male subjects is taken as 100 per cent. When this is done, it is found that cases of ulcer which have a relatively low acid often have a high volume, so that the total secretion falls in the high range, whereas cases of carcinoma almost invariably have a low total secretion. Eighty-seven and one-tenth per cent of male patients with gastric ulcer and 92.5 per cent of the male patients with duodenal ulcer had total secretions above, while 100 per cent of the male patients with carcinomas had total secretions below the normal mean for age.

#### MISCELLANEOUS DATA

There were 30 cases of pernicious anemia which showed complete anacidity. In 22 cases of verified disease of the gallbladder, the range of acidity and of volume was so wide that no diagnostic conclusions could be drawn, a finding not in harmony with the claim so often made that disease of the biliary tract is associated with subnormal gastric secretion. None of the other groups of cases was large enough to analyze.

#### COMMENT

The present study is the first to be based on a large series (nearly 1,000) of standard histamine tests carefully executed by a trained personnel. The results, therefore, should be definitive, and it is hoped that the question of normal standards, as well as the findings in certain disorders, are now settled for all time. Furthermore, these are the only extensive observations on the volume of gastric secretion in man, a matter of prime importance from both the physiologic and the chemical standpoint,<sup>13</sup> as the facts that have been presented clearly show. It is not the present purpose to debate the relative merits of various tests of gastric function, as the question has recently been fully discussed from this clinic.<sup>14</sup> Discussion, furthermore, seems pointless since many of the recent papers represent not a critical examination of the facts, but special pleading by men who are obviously biased by reason of sentiment or tradition in favor of one or another of the older procedures. I shall dismiss the question, then, by reiterating that the histamine test is the only available procedure which fulfils the recognized criteria of an adequate functional test, it is standardizable, it imposes a maximum load on function, and it yields pure juice suitable for quantitative measurement.

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13 Bloomfield, A. L., and Keefer, C. S. Gastric Motility and the Volume of Gastric Secretion in Man, *J. Clin. Investigation* 5: 295, 1928, footnote 4.

14 Bloomfield, A. L. Clinical Aspects of Gastric Secretion, *Ann. Int. Med.* 6: 307, 1932.

With regard to normal standards, the previous observations of Pollard and Bloomfield, Vanzant and Alvarez and others are confirmed and extended. The outstanding fact is that there is no narrow zone into which the secretions of all healthy people fall, acid values from 0 to 160 and ten minute volumes of from 10 to 100 cc are encountered. There is, to be sure, a peak to the distribution curves, but it seems clear that hypo-acidity and hyperacidity as pathologic clinical states must be abandoned. The differences between the sexes and the fall in the rate of secretion with advancing years, especially in male subjects, are phenomena of physiologic interest and also of great clinical importance, since they clearly must be taken into account in assessing gastric function in disease.

Since the normal range is so great, it becomes clear that only when the case is extreme can information of consistent diagnostic value be obtained from measurements of gastric secretion, in peptic ulcer, cancer of the stomach and pernicious anemia, such is the case, but fruitful application of these studies is obviously limited in clinical practice, and further minor modifications of technic are not likely to be of much more help.

#### SUMMARY

An analysis has been made of 988 consecutive histamine test meals. Six hundred and eighty-four of the patients showed no evidence of disease, and standards of normal for gastric acidity and volume of secretion were derived from these data.

The mean total acidity for male subjects ranged from 101.1 units at the age of 25 to 67.1 units at the age of 65. The mean total acidity for female subjects ranged from 82.2 units at the age of 25 to 66.7 units at the age of 65. This included normal subjects who had anacidity. In the case of the male subjects, there was a definite correlation between age and acidity.

The mean maximum ten minute volume of secretion for male subjects ranged from 39.7 cc at the age of 25 to 24.9 cc at the age of 65. The mean volume of secretion for the female subjects ranged from 33.1 cc at the age of 25 to 21.7 cc at the age of 65. There was a definite correlation between age and volume in the two sexes.

In both sexes the total gastric secretion declined with age at about the same rate.

There was a steady increase in the incidence of anacidity from youth to old age, and at all age periods up to 60 the incidence was higher in female than in male subjects. The incidence for the normal male subjects was 10.7, and for the normal female subjects, 14.1 per cent.

In 130 cases of duodenal ulcer, 91.3 per cent of the subjects had a total acidity and 79.2 per cent had volumes of secretion higher than the mean values of normal persons of the same age and sex.

In 36 cases of gastric ulcer, 91.7 per cent of the patients had a total acidity and 75 per cent had volumes of secretion higher than the mean values of normal people of the same age and sex.

In 56 cases of carcinoma of the stomach, the incidence of anacidity was 69.6 per cent. In the 56 cases, there was only 1 patient who had an acidity and 3 who had volumes above the mean normal value for the same age and sex.

Eighty-seven and one-tenth per cent of male patients with gastric ulcer and 92.5 per cent of male patients with duodenal ulcer had total secretions above the normal mean for age, and 100 per cent of male patients with carcinomas had total secretions below this mean.

The diagnostic value of the histamine test meal in differentiating benign from malignant lesions of the stomach is discussed.

In a miscellaneous group of cases, no evidence could be found that any particular disease, except pernicious anemia, was associated with a characteristic type of gastric secretion.



# PEPTIC ULCER

## VIII RESULTS OF MEDICAL AND SURGICAL TREATMENT OF PATIENTS IN RURAL DISTRICTS AND IN SMALL TOWNS

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During recent years many statistical studies of peptic ulcer have appeared in the literature. Most of them have dealt with patients in the larger cities. At the University of Virginia Hospital, however, the majority of the patients come from rural districts and the smaller towns and cities. Many of the patients present peculiar problems because of their economic and social status, their mode of living and their dietary habits and limitations. Mountaineers, farmers cultivating poor soil and others unaccustomed and often unable to procure any but the roughest sort of diet tax the ingenuity of the internist who would treat them medically for peptic ulcer.

In this study an attempt has been made to evaluate the late results of the medical and surgical treatment of all patients with peptic ulcer seen in the hospital during a ten year period, 1918 to 1928. For the purpose of comparison, a brief summary of the literature of statistical and follow-up studies precedes the presentation of the data.

### MEDICAL STATISTICS

Of especial interest is the recent report made by Brown,<sup>1</sup> an associate of the late Dr. Sippy. He surveyed all their cases in the Presbyterian Hospital, Chicago, from 1912 to 1928 and also included 167 cases of former associates. Cases with an inconclusive diagnosis were excluded. Questionnaires were sent to 1,900 patients, and 1,224 cases thus followed were studied carefully. Of this number, 917 (75 per cent) were in men and 307 (25 per cent) in women. The average age at which symptoms commenced was 35 years. The average time between the onset of symptoms and the first examination was seven and one-half years. The patients complained of actual pain in 51 per cent of cases and of discomfort in 49 per cent, both usually sharply localized in the epigastrium. Spontaneous vomiting occurred in 17 per cent of the

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From the University of Virginia

1 Brown, R. C. The Results of Medical Treatment of Peptic Ulcer, J. A. M. A. **95** 1144 (Oct 18) 1930

cases and hemorrhage, either prior to or after treatment, in 24 per cent. Perforation occurred in 4 per cent.

Of the 1,224 patients successfully followed, 1,130 had been treated medically and 94 (7.7 per cent) surgically. No report was made of the latter group, but of those treated medically, 49.5 per cent were graded as cured, 16.7 per cent as satisfactorily improved and about 10 per cent as moderately improved, in 20 per cent there had been a failure to obtain relief by medical measures.

Blown conceded that the "cured" patient might have a recurrence of symptoms at any later time. He noted that the early cases offered the best chance for a cure. In the cases seen later, scarring at the site of ulceration was common, obstruction to the outlet of the stomach not infrequent and the results of medical treatment, therefore, often unsatisfactory. Obstruction due solely to acute inflammatory tissue was usually relieved by treatment in two or three weeks. Failure to respond denoted scarring, which he said should be an indication for surgical intervention. He concluded that in addition to the 7.7 per cent of patients who were treated surgically, the 20 per cent of patients in whom medical treatment had failed should have received surgical treatment. In his opinion the most serious problem to be faced is the inability of physicians to insure an individual with peptic ulcer against recurrence.

While the most carefully controlled treatment initiated by rest in bed is prescribed by the Sippy regimen, many clinicians now feel that most patients with peptic ulcer respond almost as well to a less rigorous and ambulatory treatment. Blackford and Bowers<sup>2</sup> of Seattle studied two similar groups of patients, one hospitalized, the other ambulatory, and found almost equally good results, about 60 per cent satisfactory improvement, in both groups.

Lynch,<sup>3</sup> in analyzing 944 cases of peptic ulceration at the Montreal General Hospital, found that the incidence of peptic ulcer was 1.45 per cent of the total hospital admissions. He stated that 72 per cent of the patients had been treated medically and 28 per cent surgically. Of those treated medically, 153 gastric and 165 duodenal ulcers had been treated by the Lennhartz regimen, with 65 per cent and 78 per cent satisfactory results, respectively, while 57 gastric and 137 duodenal ulcerations had been treated by the Sippy method, with 60 per cent and 81 per cent satisfactory results, respectively. In the cases in which hemorrhage was a complication he advised operative treatment as soon

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2 Blackford, J. M., and Bowers, J. M. A Comparison of the Late Results of Ambulatory and Hospital Treatment of Peptic Ulcer, *Am J M Sc* **177** 51, 1929.

3 Lynch, R. Analysis of Ulcer of the Stomach and Duodenum, *Canad M A J* **17** 677, 1927.

as the patient could be adequately rehabilitated, usually within a period of from four to five weeks

Miller, Prendergrass and Andrews,<sup>4</sup> of Philadelphia, reported results very similar to those previously quoted. They noted that while the acidity of aspirated gastric chyme tended to be high in patients with peptic ulcer, nevertheless many apparently normal persons had an equally high gastric acidity. This is in accord with similar results previously published by me.<sup>5</sup>

Eusterman,<sup>6</sup> in discussing Brown's study, mentioned Nielson, Crohn, Greenough and Joslin as averaging about 27 per cent "cures" in their cases of medically managed peptic ulcer. He said that of 520 patients treated medically at the Mayo Clinic, 35 per cent considered themselves cured. An additional 43 per cent were definitely improved and lost no time from work.

Many have recognized that while the medical management of ulcerations may present striking immediate results, the later results are less encouraging. Einhorn and Crohn,<sup>7</sup> in a follow-up study of 100 patients one year after treatment classified 67 per cent as cured and 22 per cent as much improved. After four years, however, only 27 per cent could be included as cured, while 23 per cent were improved.

Short,<sup>8</sup> in a comprehensive review of the statistical literature of peptic ulcer from England, America and several European countries, made the following summary:

Given the best medical treatment three out of four cases of gastric or duodenal ulcer, probably more, will become symptom free. Only 40 per cent of these patients will remain well and from 15 to 19 per cent will be dead in about 10 years. Early cases do well, long-standing cases badly.

#### SURGICAL STATISTICS

In 1930, the American Surgical Association conducted a symposium on the surgical treatment of peptic ulcer. Many interesting and important facts were elicited and opinions crystallized. St John,<sup>9</sup> in report-

4 Miller, T. G., Prendergrass, E. P., and Andrews, K. S. A Statistical Study of Clinical and Laboratory Findings in Gastric and Duodenal Ulcer, with Special Reference to Roentgenologic Data, *Am J M Sc* **177** 15, 1929.

5 Morton, C. B. Observations on Peptic Ulcer. VI. Preliminary Report of Clinical Experiments with Gastro-Duodenal Analysis, *Am J M Sc* **177** 65, 1929.

6 Eusterman, G. B. Discussion of Brown.<sup>1</sup>

7 Einhorn, M., and Crohn, B. B. Follow-Up of One Hundred Cases of Gastroduodenal Ulcer Treated by Medical Means, *Am J M Sc* **172** 691, 1926.

8 Short, A. R. The Treatment of Gastric and Duodenal Ulcer. A Statistical Inquiry, *Brit M J* **1** 435, 1931.

9 St John, F. B. A Follow-Up Study of the Results in Surgical Therapy for Gastric and Duodenal Ulcer, *Ann Surg* **92** 597, 1930.

ing the results at the Presbyterian Hospital, New York City, called attention to the fact that "It must be borne in mind in comparing surgical and medical results that surgery in most clinics today in simple ulcer is only instituted at the point where medicine has failed"

Balfour<sup>10</sup> reported from the Mayo Clinic the results of gastroenterostomy in 500 cases of duodenal ulcer and 100 cases of gastric ulcer followed for a period of from five to ten years. In the patients with duodenal ulcer males outnumbered females five to one. There was an operative mortality of only 1.8 per cent, with 4.28 per cent of deaths within five years. The follow-up revealed satisfactory relief from symptoms in 87 per cent of cases. There was complete relief in 69 per cent, fair relief in 18 per cent and failure in 13 per cent of the cases. Recurrent ulceration was encountered in 4.07 per cent of 491 patients, including the occurrence of gastrojejunal ulcer in 3.26 per cent (16 cases), incidentally only about one-half the mortality rate following gastrectomy.

In the patients with gastric ulcer the operative mortality was 3 per cent, with 17 per cent of deaths within five years. The follow-up revealed satisfactory results in 79 per cent of the cases. There was complete relief from symptoms in 50 per cent, fair relief in 4 per cent and poor results in 17 per cent of the cases. Carcinoma was discovered later in 6 of the patients.

In a previous paper by Balfour<sup>11</sup> giving his results of gastroenterostomy in 100 physicians, the operative mortality was 1.82 per cent in the duodenal and 4.7 per cent in the gastric group. Eight and one half years after operation the result was satisfactory in 93 per cent of the patients.

Judd and Hazeltine<sup>12</sup> reported from the Mayo Clinic the results of operations for excision of ulcer of the duodenum including excision of part of the pyloric ring. Of 464 patients operated on from 1924 to 1928, 369 were traced. The operative mortality was only 0.43 per cent. The results were satisfactory in 90 per cent of the cases, and in only 8.1 per cent was there no benefit. Deaver and Burden<sup>13</sup> also advocated operation on the pyloric ring in the surgical treatment of duodenal ulceration.

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10 Balfour, D. C. Results of Gastroenterostomy for Ulcer of the Duodenum and Stomach, *Ann Surg* **92**: 558, 1930.

11 Balfour, D. C. The Results of Operation for Duodenal Ulcer in Physicians, *Ann Surg* **86**: 691, 1927.

12 Judd, E. S., and Hazeltine, M. E. The Results of Operations for Excision of Ulcer of the Duodenum, *Ann Surg* **92**: 563, 1930.

13 Deaver, J. B., and Burden, V. G. Further Experience with Resection of the Anterior Half of the Pyloric Sphincter, *Ann Surg* **92**: 533, 1930.

Gatewood<sup>14</sup> from the Presbyterian Hospital, Chicago, reported 163 cases of peptic ulcer in which the patients were treated surgically, with an operative mortality of 18 per cent. Of this group, 82 per cent were either entirely well or greatly improved, 85 per cent died subsequently of gastric disease, while 48 per cent died of other causes.

Horsley,<sup>15</sup> from Richmond, reported 160 cases in which the patients were treated by various operations. His total operative mortality was 6 per cent, and 59 per cent of the patients were either symptom-free or greatly improved after operation.

Argument concerning the rôle of gastrectomy in the treatment of duodenal ulceration has been frequent since Lewishorn's<sup>16</sup> statistics from the Mount Sinai Hospital, New York, revealed the occurrence of gastrojejunal ulcer in 34 per cent of their patients who had been treated by gastro-enterostomy and Berg<sup>17</sup> published his results of partial gastrectomy. Berg's operative mortality was 69 per cent and a gastrojejunal ulceration occurred in only 11 per cent of the cases. With these exceptions the results were practically 100 per cent satisfactory.

Finney and Hanrahan<sup>18</sup> reported the cases in which surgical treatment was given at the Johns Hopkins Hospital, there were a general operative mortality of 86 per cent and 84.6 per cent of satisfactory results.

In discussing gastro-enterostomy, Balfour<sup>19</sup> said

When the American Surgical Association presents such figures as these from various members and they all run between 85 and 90 per cent (good results) it is convincing evidence of what can be accomplished in chronic duodenal ulcer by indirect operation alone.

#### PEPTIC ULCER AT THE UNIVERSITY OF VIRGINIA HOSPITAL

*Incidence*—During the ten year period, from 1918 to 1928, the total combined admissions to the medical and surgical services numbered 32,938. In that number of patients the diagnosis of peptic ulcer of the stomach or duodenum was recorded in 370 instances, an incidence of 1.12 per cent (table 1).

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14 Gatewood. The Immediate Mortality and Late Results of Operations for Peptic Ulcer, *Ann Surg* 92:554, 1930.

15 Horsley, J. S. The Immediate Mortality and Late Results of Operations for Gastric and Duodenal Ulcers, *Ann Surg* 92:545, 1930.

16 Lewishorn, R. The Frequency of Gastrojejunal Ulcers, *Surg, Gynec & Obst* 40:70, 1925.

17 Berg, A. A. The Mortality and Late Results of Subtotal Gastrectomy for the Radical Cure of Gastric and Duodenal Ulcer, *Ann Surg* 92:340, 1930.

18 Finney, J. M. T., and Hanrahan, E. M., Jr. Results of Operations for Chronic Gastric and Duodenal Ulceration, *Ann Surg* 92:620, 1930.

19 Balfour, D. C. *Ann Surg* 92:638, 1930.

Among the 370 patients admitted there were 286 with ulcer of whom 220 had duodenal and 66 gastric ulceration. Two were suspected of having both gastric and duodenal ulceration. There were 247 patients of the white and 39 of the Negro race. Comparing these figures with the total number of white and Negro patients admitted to the hospital, there was almost twice as high an incidence of peptic ulcer in the white as in the Negro race. There were 219 males and 67 females. The most frequent age incidence was the decade between 30 and 40 years. The patients were almost equally divided as to town and rural residence, with a slight preponderance of those living in strictly rural districts. In more than half of the patients the symptoms had been present for more than two years.

*Complications*—Of the complications, hemorrhage was the most frequent, occurring as gross blood in the vomitus or stools in 68 cases.

TABLE 1—*Incidence of Cases of Peptic Ulcer at University of Virginia Hospital*

Year	Hospital Admissions			Peptic Ulcer Admissions		
	Medical	Surgical	Total	Medical	Surgical	Total
1918	1,600	1,715	3,315	23	9	32
1919	1,120	1,921	3,041	16	8	24
1920	1,084	1,947	3,031	9	6	15
1921	1,230	2,245	3,475	16	5	21
1922	1,438	2,196	3,634	25	13	38
1923	1,594	2,372	3,966	21	15	36
1924	1,390	2,203	3,593	45	21	66
1925	1,549	1,461	3,010	29	16	45
1926	1,450	1,314	2,764	37	9	46
1927	1,594	1,515	3,109	38	9	47
Totals	14,049	18,889	32,938	259	111	370

or almost one fourth of the patients. Obstruction and perforation were much less frequent.

*Treatment*—Medical treatment was employed in 196 (68.6 per cent) of the cases and surgical treatment in 90 (31.4 per cent). Operation was advised for 16 (5.5 per cent) additional patients, but they preferred medical management. Except in cases in which there was marked obstruction at the pylorus, in some cases of hemorrhage and in all of those with perforation of the ulcer, medical treatment was given a trial before operation was advised.

Of the deaths in the hospital, 6 occurred during medical treatment and 8 among the 90 patients treated surgically, including the 24 with perforated ulcers (table 2).

*Results*—Of the 272 patients discharged from the hospital 190 had been treated medically and 82 surgically. Follow-up letters were sent to each of them. In some instances the patients reported on their condition by a personal interview, in some long letters in addition to the completed questionnaire were forwarded, and in others merely the com-

TABLE 2—Comparative Data for Patients with Gastric and Duodenal Ulcers

		Site of Ulceration		
		Gastric	Duodenal	Totals
Number		66	220	286
Race	{ White	57	190	247
	{ Negro	9	30	39
Sex	{ Male	42	177	219
	{ Female	24	43	67
Age (years)	{ 1-20	4	10	14
	{ 21-30	13	50	63
	{ 31-40	16	67	83
	{ 41-50	13	47	60
	{ 51 plus	20	46	66
Residence	{ City or town	33	104	137
	{ Country	33	116	149
Duration of symptoms	{ 1 month or less	12	13	25
	{ 1 to 6 months	10	25	35
	{ 6 months to 1 year	4	22	26
	{ 1 to 2 years	7	23	30
	{ 2 years or more	33	137	170
Complications	{ Obstruction	4	33	37
	{ Hemorrhage	19	49	68
	{ Perforation	9	15	24
Treatment	{ Medical	43 (65%)	173 (69 6%)	196
	{ Surgical	23 (35%)	67 (30 4%)	90
	{ Surgery refused	5	11	16
Hospital result	{ Medical death	4	2	6
	{ Surgical death	4	4	8
	{ Discharged	58	214	272
Follow up	{ Letters sent	58	214	272
	{ Replies	33	131	164

TABLE 3—Comparison of the Results of Medical and Surgical Treatment

Site of ulceration Number of patients followed up (164)		Method of Treatment					
		Medical		Surgical			
		Gas tric 25	Duo denal 85	Gas tric 8	Duo denal 46		
Subsequent Deaths	{	Unqualified	3	2	0	2	
		Not from ulcer	0	2	0	2	
		From ulcer	0	2	0	0	
		From carcinoma of stomach	3	0	0	0	
		From probable carcinoma of stomach	0	0	1	0	
Patients Still Living Jan 1 1930	{	General result	Excellent	2	6	4	26
			Good	9	31	3	10
			Fair	6	28	0	3
			Poor	2	14	0	3
	{	Symptomatic result	No symptoms	5	17	4	24
			Occasional symptoms	13	48	3	14
			Frequent symptoms	1	14	0	4
	{	Economic result	Full time work	12	54	6	37
			Part time work	7	20	1	3
			Unable to work	0	5	0	2
	{	Dietary restriction	None	7	21	4	25
			Occasional food intolerance	5	13	2	11
			Necessary occasionally	4	13	1	3
			Necessary constantly	3	32	0	3
	{	Alkali required	None used	9	23	4	29
			Occasionally	9	36	3	10
			Frequently	1	20	0	3
	Subsequent operation necessary		0	6	0	0	
	Subsequent gastrojejunal ulcer		0	0	0	3	

pleted questionnaire was returned. Altogether 164 patients were followed, the time that had elapsed since treatment varying between twelve years and two years.

The results were recorded without knowledge at the time as to whether medical or surgical treatment had been employed. An effort was made to evaluate the symptomatic and economic results and to correlate this with the necessity of adhering to dietary restriction and the use of alkalis. All these factors were then estimated and the patient finally classified as having obtained excellent, good, fair or poor general results (table 3).

As subdivided into groups the number of cases in each is too small to reduce to accurate percentages. In order to express the figures, however, certain proportions may be stated. Of the medically treated, living patients, slightly more than one half with gastric ulceration and a few less than one half with duodenal ulceration obtained satisfactory results. In very few in either group, however, were the results classified as excellent. Of 25 patients with gastric ulcer 3 had died subsequently of known carcinoma of the stomach and 3 of unspecified causes. In 85 patients with duodenal ulcer 2 had died from the ulcer, 2 from other causes and 2 from unspecified causes. Subsequent operation had been performed in 6 of the patients.

Of the surgically treated living patients, all of those with gastric ulceration and more than three fourths of those with duodenal ulceration obtained satisfactory results. Half in the gastric and more than half in the duodenal group were classified as having obtained excellent results. Of 8 patients with gastric ulcer 1 had died subsequently of suspected carcinoma of the stomach. In 46 patients with duodenal ulcer, 2 had died from other causes than ulcer and 2 from unspecified causes. There were 3 patients in whom gastrojejunal ulceration apparently had developed.

Comparing the symptomatic results, there was definitely more complete relief from surgical than from medical treatment. The same was true of the economic results. As regards the necessity for dietary restriction and the use of alkalis, it was quite apparent that the majority of those treated medically had to adhere more or less strictly to dietary regulation and had to employ alkalis fairly regularly, while the majority of those treated surgically were able to eat more or less normally and seldom had to resort to the use of alkalis. Many of the patients treated medically had been readmitted to the hospital on two or more occasions for additional intensive treatment because of a persistence or recurrence of distressing symptoms. Several of them finally came to operation at the University of Virginia Hospital and have been included in these



statistics as surgically and not medically treated patients. As already mentioned, 6 of the patients followed and recorded as medically treated in this hospital reported such an unsatisfactory result that surgical treatment had been necessary and had been administered elsewhere.

#### COMMENT

The incidence of peptic ulceration among the patients of the University of Virginia Hospital was slightly lower than that given by Lynch of the Montreal General Hospital.

The larger number of admissions (370) than patients (286) is accounted for in the main by patients treated medically who returned during the ten year period for additional courses of intensive medical treatment or surgical intervention because of the persistence or recurrence of symptoms.

There were a little less than three and one-half times as many duodenal as gastric ulcers. This is considerably lower than the usually quoted four or five to one ratio. The most frequent incidence of the disease in the third decade of life is similar to that commonly observed. While the patients were practically equally divided as to town and country residence, it may be said that practically all the patients led a rather rural life, relatively few of them coming from truly urban communities.

The tabulations revealed that 31.4 per cent of all the patients with peptic ulcer had been treated surgically, while only 68.6 per cent had persisted with medical management. Further analysis revealed that 69.6 per cent of the patients with duodenal ulceration and 65 per cent of those with gastric ulceration had been treated medically, while 30.4 per cent of those with duodenal ulceration and only 35 per cent of those with gastric ulcer had been treated surgically. Balfour<sup>20</sup> stated that during 1931 at the Mayo Clinic 30 per cent of the inflammatory lesions of the duodenum were treated surgically. He did not state the percentage in gastric ulcer but said that

It is imperative, however, to realize that by no method of examination can the character of such lesions be positively identified. If, therefore, ulceration of the stomach does not show prompt response (roentgenologically) to medical treatment in ten days or two weeks, operation should be advised, and when efficiently carried out, it offers excellent prospect of permanent control of the disease.

Lahey<sup>21</sup> recently expressed a similar policy. The fact that 3 of 25 patients who were treated medically for gastric ulceration later died of

20 Balfour, D. C. Annual Report of Operations on the Stomach and Duodenum for 1931, Proc. Staff Meet., Mayo Clin. **7**: 99 (Feb. 17) 1932.

21 Lahey, F. H. The Selection of Gastric Ulcers for Surgery, Surg., Gynec. & Obst. **54**: 251 (Feb.) 1932.

known carcinoma of the stomach is a sufficient reminder of the importance of the ablation of all gastric ulcers that do not respond quickly and quantitatively, as demonstrated roentgenologically, to medical management. Many circumscribed carcinomatous gastric lesions masquerade as benign ulcer, and only by prompt surgical intervention will the appallingly high mortality of gastric carcinoma be lowered. To advise surgical removal of the ulcer for these patients is the duty and responsibility of both the internist and the surgeon.

That almost as many deaths occurred in the hospital while patients were under medical as under surgical treatment indicates that neither is devoid of risk. This fact is even more apparent when it is considered that in the 90 patients with peptic ulcer treated surgically perforation of the ulcer had occurred in 24 instances.

Analysis of the tabulations reveals that in the type of patient seen at the University of Virginia Hospital the results of surgical treatment are distinctly better than those of medical treatment. The economic and social status of many of these persons, their mode of living and their dietary habits and limitations may account in part for the fact.

To advise and outline a medical regimen that of necessity must contain some of the dietary niceties of life and the preparation of which presupposes certain further culinary proficiency is not difficult. However, it may often be practically impossible for persons economically and otherwise handicapped to adhere to this regimen.

In conclusion, this study leads me to believe that the management of peptic ulcer must be prescribed with due regard to the site of the lesion and the type of patient afflicted.

For patients with duodenal ulcer who are economically able and sufficiently intelligent and willing to adhere strictly to a prolonged medical regimen, such treatment should certainly be employed, unless and until complications or surgical indications supervene. For those, however, who are economically unable or not sufficiently intelligent or willing to cooperate, the prescribing of medical treatment is too frequently a waste of time and delays eventual rehabilitation. Such circumstances well might be given consideration among the generally accepted surgical indications—hemorrhage, obstruction and perforation.

An ulceration in the stomach might better be considered an indication for surgical treatment until proved otherwise. In young persons with small uncomplicated gastric ulcerations and roentgenologic evidence of response to medical treatment within two or three weeks, surgical intervention would seldom be warranted. As the age of the patient increases, however, the danger of even small gastric ulcerations being malignant increases, and greater caution should be exercised. In the

middle-aged or older patient, even the small gastric ulceration, unless it shows roentgenologically prompt diminution in size under treatment, and assuredly the larger ulceration are potentially malignant and should be excised

#### SUMMARY

A brief review of some of the more recent statistical studies of persons medically and surgically treated for peptic ulcer was made for purposes of comparison with a similar study of patients with peptic ulcer at the University of Virginia Hospital. At that institution, from 1918 to 1928, 286 persons were treated, 66 for gastric and 220 for duodenal ulcerations. Most of the patients were from rural districts and the smaller towns and cities and presented peculiar problems because of their economic status, mode of living and dietary habits and limitations.

The general statistics were similar to those generally given, except that there was twice as high an incidence of peptic ulceration in the white as in the Negro race, and that the ratio of duodenal to gastric ulceration was only about three and one-half to one rather than a higher ratio, as much as ten to one, given by some writers.

The late results (after from two to twelve years) of medical and surgical treatment in 164 patients were ascertained by follow-up. They were classified under excellent, good, fair and poor general results after the symptomatic and economic results were estimated and the dietary limitation and the use of alkali necessitated were recorded.

Of 33 patients with gastric ulcers successfully followed, 25 had been treated medically and 8 surgically. Of the 25 treated medically, 3 had subsequently died of carcinoma of the stomach and 3 of unspecified causes. Of the 19 survivors, slightly more than one half reported satisfactory results. Of the 8 treated surgically one had subsequently died of some gastric disorder, but all of the 7 survivors reported satisfactory results.

Of 131 patients with duodenal ulcers successfully followed, 85 had been treated medically and 46 surgically. Of the 85 treated medically, 2 had subsequently died from the ulcer, 2 from other causes and 2 from unspecified causes. Of the 79 survivors a few less than one half reported satisfactory results, and 6 had subsequently resorted to surgical treatment because of the persistence of symptoms. Of the 46 treated surgically, 2 had died subsequently of unspecified causes and 2 of causes other than ulcer. Of the 42 survivors more than three fourths reported satisfactory results. In 3 patients gastrojejunal ulceration apparently developed.

In the type of patient studied the results of the medical management of peptic ulcer were appreciably less satisfactory than the results of the surgical treatment. To obtain satisfactory results, those treated medically had had to adhere much more strictly to dietary regulation and the use of alkalis than those treated surgically. Some criteria for the choice of treatment have been briefly alluded to

# EFFECT OF STIMULATION OF VISCERAL NERVES ON CORONARY FLOW IN DOGS

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In this paper, the results of a study of the effect of stimulation of the visceral nerves and distention of the stomach, the lower part of the esophagus and the gallbladder will be reported. The results of such a study are obviously not only of academic interest but also of clinical interest, because of the relative frequency of attacks of coronary thrombosis and angina pectoris after the ingestion of food and accompanying gaseous distention.

The study of the effect of visceral excitation on coronary flow appears at first sight to be simple and clearcut. However, because a number of other factors are concerned in regulating the coronary circulation, the problem is somewhat involved. The chief factor regulating coronary flow, which has been recognized as such by all investigators of coronary circulation, is blood pressure<sup>1</sup>. The rise and fall of blood pressure and the rise and fall of coronary flow are directly parallel. The heart rate appears to have no effect on coronary flow. Some observers have noted a decreased flow with an increased heart rate produced by means of an increase in temperature. But since it is known that temperature has a direct effect on the coronary vessels and since other methods of changing the heart rate, that is, by induction shocks and by heating and cooling the sino-auricular node, are without effect, it seems that there is no pure frequency change which directly influences coronary flow. Whatever the effect of heart rate on coronary flow may be, it seems to be determined by changes in the duration and the strength of ventricular contraction. Increased "tone" of the heart is thought not to increase the flow. But "dilatation" of the heart does increase it. Lack of oxygen and an increase in carbon dioxide augment the flow. Metabolites appear to have no effect in the heart-lung preparation. Whether or not they do in the whole animal has, as yet, not been determined. Another point that must be taken into consideration is that a progressive increase in coronary flow frequently occurs during

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<sup>1</sup> Anrep, G. V. *Physiol. Rev.* **6**: 596, 1926.

the course of an experiment. We have observed this as have others. It has been ascribed to a loss of "tone" or "dilatation" of the heart which favors an increased coronary flow.<sup>1</sup>

The coronary arteries have a rich innervation. The denervation experiments of Woolard<sup>2</sup> show that the coronary arteries up to their finer ramifications receive a double innervation. The larger arterial branches are innervated by the vagus and sympathetic fibers to about an equal extent, while the innervation of the smallest branches is predominantly vagal in origin.

The aforementioned points were kept in mind as factors to be taken into consideration in a study of the effect of excitation of visceral nerves and organs on coronary flow.

The method of Morowitz and Zahn<sup>3</sup> was used on dogs. The blood drainage of the heart flowing into the coronary sinus (60 per cent of the entire amount) was collected by means of a Morowitz cannula, as modified by Gilbert and Fenn,<sup>4</sup> which was placed in the sinus. The cannula was connected through rubber tubing to an inlet at the bottom of a large test tube, the tube being provided with a similar outlet and with a float. The inflow causes the float to rise, making a tracing on the smoked drum at the same time as blood pressure and time records are made. The tube was emptied when full, and the blood returned to the animal through the femoral vein after passage through loops of glass coils immersed in water at a temperature slightly higher than that of the body so as to keep the temperature of the blood as nearly normal as possible. The rate of return of the blood was regulated so that the inflow would be about as rapid as the outflow. Heparin (12 mg per pound of body weight) was used to prevent coagulation. Pentobarbital sodium anesthesia was used. The heart was kept from drying by closing the chest except when the nerves in the chest were stimulated, and then physiologic solution of sodium chloride at 34 C (93.5 F) was applied to the heart.

#### EXPERIMENTAL RESULTS

*Stimulation of Intact Vagus Nerve Below Heart on Esophagus Above Diaphragm and on Stomach in Region of Cardia*—The intact nerve at the level of the esophagus and of the stomach was stimulated with an induced current. This was done primarily to obtain at the same time peripheral effects, contraction of the stomach and central reflex effects. In order to stimulate the intact nerve it was simply dissected free for about 1 inch (2.5 cm) and the electrodes applied. (For all electrical stimulation experiments a Harvard inductorium with two dry cells and the secondary coil at 4 cm was used.)

Twenty-six experiments were performed. There was no detectable difference in the results when the intact nerve was stimulated on the

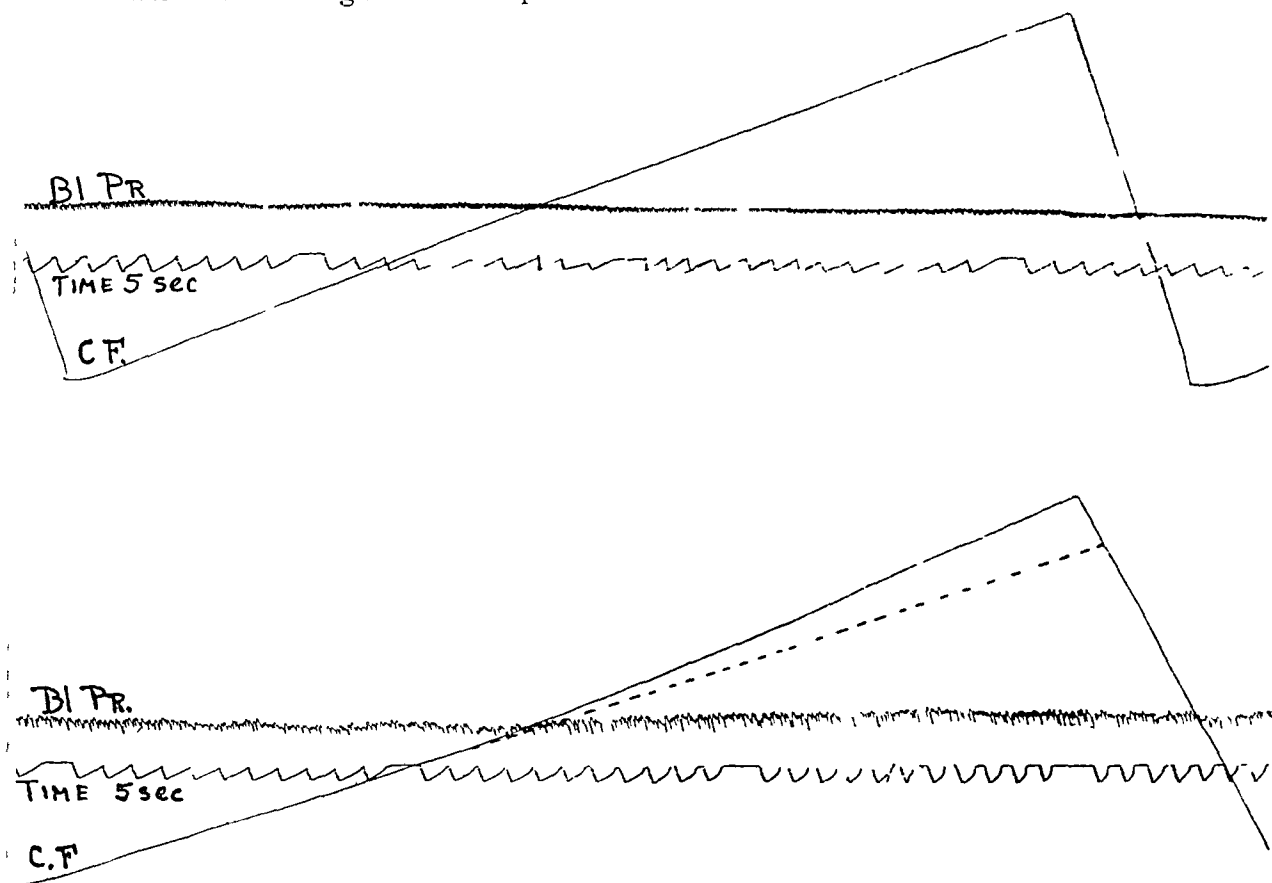
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<sup>2</sup> Woolard. J. Anat. **60** 345, 1926.

<sup>3</sup> Morowitz and Zahn. Deutsches Arch. f. klin. Med. **116** 364, 1914.

<sup>4</sup> Gilbert, N. C., and Fenn, G. K. Effect of the Purine Base Diuretics on the Coronary Flow, Arch. Int. Med. **44** 118 (July) 1929.

esophagus or on the stomach. In six experiments the blood pressure was elevated and the coronary flow, of course, increased. In two of ten experiments an increase (25 and 68 per cent) in coronary flow was associated with a fall in blood pressure. In four of five experiments the coronary flow was increased without a change in blood pressure, the range of increase being from 10 to 45 per cent. In one of five experiments the coronary flow was decreased (24 per cent) without a change in blood pressure.



#### STIM CENT END GASTRIC VAGUS

This figure shows that stimulation of the central end of the gastric vagus may lead to an increase in coronary flow. The upper tracing is the control flow. The ascending line labeled "CF" is made by the float which rises as the blood from the coronary sinus fills the tube in which the float rides. In the upper tracing it is to be noted that the float rises uniformly. In the lower tracing just after the stimulation of the vagus it is to be noted that the float rises more rapidly, denoting an increase in coronary flow.

It is evident from these results that stimulation of the intact vagus below the heart may cause an increase in coronary flow, since a decrease occurred in only one of the twenty-six experiments, and since an increase in flow was observed. Not only did no change in blood pressure occur, but in two of ten instances an increased flow resulted during a fall in blood pressure.

*Stimulation of Central End of Sectioned Vagus Nerve Below Heart*—Twenty experiments were performed as in the preceding group, except that the vagus was sectioned and the central end stimulated

In four experiments an increase in coronary flow was associated with a rise in blood pressure. In two of four experiments an increase (5 and 10 per cent) in coronary flow occurred, with a decrease in blood pressure. In one of four experiments a decrease in flow resulted with a decrease in blood pressure, and in one of four experiments a decrease in blood pressure was not associated with a decrease in flow. In three of four experiments the flow increased without a change in blood pressure, the increase ranging from 14 to 53 per cent.

These results are essentially the same as those obtained in the preceding group, and show that excitation of the gastric and esophageal vagi induces an increase in coronary flow.

*Stimulation of Right Splanchnic Nerve Below Diaphragm*—An attempt was made to stimulate the right splanchnic nerve centrally with a weak current without obtaining a rise in blood pressure, but at the same time obtaining a change in coronary flow. This could not be accomplished in all dogs. Thirteen experiments were done. In three experiments the blood pressure rose with the usual increase in coronary flow. In two of four experiments a fall in blood pressure was associated with an increase (12 and 16 per cent) in coronary flow. In two experiments an increase (20 and 52 per cent) in coronary flow was not associated with a change in blood pressure. A decrease in coronary flow was associated with a decrease in blood pressure in two experiments.

In addition to these experiments, the nerves along the cystic and common bile ducts and splenic vessels and the celiac plexus were stimulated. Invariably no change in coronary flow resulted that could not be accounted for as being due solely to a rise or fall in blood pressure.

From the results in this group of experiments it is evident that if any change in coronary flow results from stimulation of the visceral nerves which cannot be accounted for by fluctuations in blood pressure, it is always in the direction of an increase in coronary flow.

*Distention of Esophagus, Stomach and Gallbladder*—The lower end of the esophagus, the stomach and gallbladder were markedly distended by fixing a balloon in place within the lumen. Thirteen experiments were performed. Since the results were essentially the same, regardless of the viscus distended, they may be grouped. In five experiments, increase in coronary flow was associated with a rise in blood pressure. In one of four experiments, the coronary flow increased (32 per cent) in the presence of a slight fall in blood pressure. An increase (27 per cent) in coronary flow occurred in one of two experi-



ments in which there was no change in blood pressure. Decreased coronary flow occurred in one of two experiments in which the blood pressure did not change. The decrease was definite (8 per cent) and occurred when the gallbladder was distended.

*Stimulation of Peripheral Vagus in Neck After Atropine*—Although we were not directly interested in the question of the vagal control of the coronary circulation, five experiments were performed in which after the administration of atropine the peripheral left vagus was stimulated about 1 inch below the thyroid cartilage. In four of the five experiments, increased coronary flow resulted either in no change (two experiments) or in only a slight decrease in blood pressure (two experiments). In one a decrease (13 per cent) in coronary flow occurred in the presence of a slight rise in blood pressure. These results show only that a variation in the coronary response to stimulation of the vagus nerve in the dog occurred in our experiments.

#### COMMENT

We agree with Greene,<sup>5</sup> who used the same method we have employed, that it is difficult to demonstrate a decided decrease in coronary flow in the dog on stimulation of the vagus. These observations are not necessarily to be taken as contradictory to the results of Anrep and Segall<sup>6</sup> and of Wiggers,<sup>7</sup> who employed different methods for studying coronary flow. The variation in results may be due to the presence of different types of fibers in the vagus which may vary from one dog to another in regard to the number of each type in each vagus nerve trunk and the relative numbers of these fiber groups found at different levels in the vagus trunk after it leaves the ganglion nodosum. In this respect, the recent work of Morgan and Goland<sup>8</sup> is pertinent. No one has stimulated the vagus in the region of the ganglion nodosum to ascertain whether the vasoconstrictor nerves are in the vagus trunk before sympathetic fibers join it, and the fact that Wiggers after the use of atropine in the dog obtained a decrease of coronary flow on stimulating the vagosympathetic pharmacologically indicates that the vasoconstrictors may be sympathetic rather than parasympathetic.

Although we had expected to observe coronary constriction quite regularly on excitation of the abdominal viscera or nerves leading from them, we failed to do so. In only two of forty-nine experiments did we observe a decreased coronary flow on distending the viscera or on stimulating the central end of the vagi or splanchnic nerves which

5 Greene J. Missouri M. A. **28** 466, 1931.

6 Anrep and Segall J. Physiol. **61** 215, 1926.

7 Wiggers Am. J. Physiol. **24** 391, 1909.

8 Morgan and Goland Am. J. Physiol. **101** 274, 1932.

could not be accounted for by a change in blood pressure. In these two experiments the constriction was slight, being 8 and 24 per cent, when compared to the dilatation which sometimes amounted to 68 per cent. This is essentially in agreement with the findings of Greene, the only difference being that he found that if the stimulation of the sensory nerves from the abdominal viscera was intense, a diphasic reaction resulted which was characterized by coronary dilatation followed by constriction. This we failed to observe.

When we seek to interpret these results on the dog in regard to the relation of visceral distention and excitation to angina pectoris in man, we can only arrive at the same opinion expressed by Sutton and Lueth<sup>9</sup> and Greene, namely that the failure of reflex coronary dilatation under conditions which augment cardiac activity accounts for the association of angina with visceral excitation. Visceral distention and irritation increase the rate and work of the heart, and normally a reflex dilatation of the coronary vessels should occur. If dilatation does not occur, angina is likely to occur because of partial asphyxia or an inadequate supply of oxygen to the cardiac muscle. It is analogous to the concept of "effort angina," a "visceral effort angina" analogous to the so-called somatic "effort angina." We accept the theory that reflex coronary constriction may be a factor, but maintain on the basis of our results on the dog that the failure of the reflex dilator mechanism plays a more important rôle than the constrictor mechanism. In regard to the association between the ingestion of a meal and the occurrence of coronary thrombosis, it is just as likely that a portion of an atheromatous plaque might be dislodged as a result of the increased cardiac activity incident to digestion and of an attempt on the part of the coronaries to dilate as to constrict.

#### CONCLUSIONS

1 The usual result of stimulating the central end of sensory nerves innervating the upper abdominal viscera or of distending the viscera on coronary flow is an increase in flow. An unquestionable decrease in flow occurred in only two of forty-nine tests, whereas an unquestionable increase in flow occurred in nineteen of thirty-nine tests.

2 In the dog reflex coronary dilatation is more readily demonstrated than reflex constriction.

3 We are inclined to accept the view of Greene, who has performed similar experiments on the dog, namely, that the failure of the reflex coronary dilator mechanism most likely accounts for the association of angina pectoris with visceral distention or excitation.

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<sup>9</sup> Sutton, D. C., and Lueth, H. C. Pain, *Arch. Int. Med.* **45**: 827 (June) 1930.

# AURICULAR FLUTTER WITH COMPLETE AURICULO- VENTRICULAR BLOCK IN A PATIENT WITH CORONARY DISEASE

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Of singular interest is the striking abnormality of rhythm exhibited in electrocardiographic tracings in the group of cases known as auricular flutter. This peculiar rhythm is a finding strictly within the domain of electrocardiography, since the clinical signs exhibited by patients with such a condition are very difficult if not impossible of detection through any other means. The reason for diagnostic failure clinically in the majority of instances of auricular flutter are obvious to those who are at all familiar with the nature of this disturbance of rhythm. Both the ear and the palpating finger at the wrist are greeted by a perfectly regular sequence of contractions, except where there exists an inconstant degree of auriculoventricular block, in most of these the ventricular rate is only moderately accelerated. It is true that the tonal quality of the heart sounds is rather altered, but such finesse in clinical differentiation belongs to diagnostic skill and acumen of the highest order only. For all practical purposes, therefore, the recognition of auricular flutter at present rests strictly with the electrocardiogram.

It is not our purpose here to delve into the intricacies of auricular flutter as a clinical or electrocardiographic entity. We merely wish to add to the literature a very interesting and uncommon case of auricular flutter with coexisting complete auriculoventricular block in a patient with coronary disease.

## REPORT OF A CASE

*History*—H. C., a man, aged 60, a native of Germany, a shoe clerk, presented an unimportant family history, both parents having died at an advanced age. His seven brothers and sisters were all living and well. There was no history of heart disease, nephritis, cancer, tuberculosis, diabetes, insanity or chronic alcoholism. The outstanding complaints were extreme fatigue, marked shortness of breath and a peculiar sensation in the chest, which the patient described singularly well as that of a "bird flapping its wings" within it.

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His previous medical history was uneventful, except for the usual diseases of childhood. The surgical history consisted of the removal of a "growth" from his colon six or seven years before the present examination, the nature of which could not be ascertained. He was told some years ago that he had a "slow pulse." He had occasional eructations after meals. About two years ago he had one attack of diarrhea with vomiting, and was confined to bed for ten days. For the past five years he had a marked nocturia, being compelled to get up four or five times during each night. He lost about 40 pounds (18.1 Kg) in weight in the past six months, during which time fatigue became one of the most prominent symptoms.

He had been married fourteen years, but had no children, his wife always enjoyed perfect health and gave no history of any miscarriages.

He never exercises, drinks tea and coffee sparingly, is a teetotaler, and has smoked three cigars daily for the past thirty years. He has always been a poor sleeper, averaging from four to five hours of interrupted sleep a night for the past twenty years.

The illness began about six months ago when the patient was seized during the night with a severe, lancinating pain in the right side of the chest, extending roughly from the second to the seventh ribs and radiating to the back into the subscapular and right lumbar regions. Sleep was almost impossible because of the practically nightly occurrences of these seizures, which were further aggravated by paroxysms of severe and prolonged coughing. The expectoration—ordinarily greenish, viscid and copious—became streaked with blood during the last two months. He had noted a marked shortness of breath, tenderness in the epigastrium and right upper quadrant, with a sensation of weight in the abdomen. The lower extremities, from the knees down, became markedly swollen during the past three weeks, so much so that the patient was frequently forced to go to work with his shoes unlaced.

Although the nocturia had increased to such a degree that sleep was out of the question, even when free from pain, micturition became exceedingly difficult, at no time in the last three weeks did he feel that his bladder was completely emptied. Anorexia became marked, and the patient was rather apprehensive of taking food because of the distress which followed meals with almost clocklike punctuality. Constipation at this time became obstinate. About one week before the patient presented himself for examination, fatigue had become so pronounced that he was obliged to go to bed for a few days. His peace of mind was considerably disturbed by the fact that fellow employees told him that he looked thin, pale and drawn.

*Physical Examination*—The patient was 5 feet, 7 inches (170.2 cm) tall, and weighed 138 pounds (62.6 Kg). He was chronically ill and cachectic in appearance, with marked cyanosis of the lips and mucous membranes. The skin was free from eruption, and was cold and clammy to the touch. The flabby state of his musculature indicated a recent loss of weight. Oral examination revealed marked dental sepsis. The nasopharynx was normal. The tongue was geographic and thickly coated, it protruded in the midline, and no fissures, atrophy or tremors were noted. The larynx was freely movable, the thyroid gland was not enlarged and was normal in consistency. There was clear transillumination of all sinuses. The eyes reacted to light and in accommodation, the pupils were regular, and both palpebral fissures were equal. There was no exophthalmos, nystagmus or strabismus, the conjunctivae were moderately injected. The fundi disclosed moderately increased tortuosity of the arteries. All superficial glands were negative. The reflexes were negative except for moderately increased knee jerks. The blood pressure taken repeatedly averaged 150 systolic over 60 diastolic.

The heart was markedly enlarged to percussion in all its diameters, but especially in the region of the great vessels. All heart sounds were muffled and distant. The second sounds at the aortic and pulmonic areas, although markedly subdued, were equal in intensity. There were no murmurs, shocks or thrills. The rhythm was perfectly regular with a ventricular rate of 38 beats per minute, there was no apparent pulse deficit. The rate was uninfluenced by a very moderate exercise test (spirometer), although the patient showed a marked dyspneic reaction following it, pointing to a serious loss of myocardial reserve.

The chest was of the emphysematous type, there were no abnormal pulsations visible or palpable. Many moist râles were heard at the bases of both lungs posteriorly.

Of interest is the examination of the abdomen. It was distended, tympanitic and decidedly tender to pressure. A hard unyielding mass was felt in the epigastrium, this seemed to be confluent with the liver and spleen, the lower border of which could be palpated with ease on deep inspiration. (In view of the past surgical history, we felt that this mass was metastatic in character.) The liver itself was very large and exhibited weak systolic pulsations, its increase in size, however, was due mostly to cardiovascular stasis.

The genito-urinary tract disclosed no abnormalities except an exceedingly large and boggy prostate. Large protruding and engorged hemorrhoids were present.

The lower extremities were swollen and pitted on pressure.

Fluoroscopic examination fully corroborated the findings in the chest. The transverse diameter of the chest measured 30 cm, with a maximum transverse cardiac diameter of 19.5 cm. The pulmonary fields were essentially clear. Diaphragmatic excursions were weak, small and halting, no adhesions were noted. The aortic shadow was markedly widened.

*Laboratory Data*—The Wassermann and Kahn tests were negative. The urine showed 2 plus albumin with occasional granular casts and frequent pus cells. Many calcium oxalate crystals were noted. The blood count showed a hemoglobin of 56 per cent, with 3,200,000 red blood cells, there were 6,800 white blood cells and the differential count showed 62 polymorphonuclears, 26 lymphocytes, 11 mononuclears and 1 eosinophil. All cells showed marked poikilocytosis.

Chemical analysis of the blood showed a slightly increased urea nitrogen of 22.5, creatinine, 1.6 and sugar, 91 mg, per hundred cubic centimeters.

Any interesting points which may have been brought out in the personal or physical history of this patient are far overshadowed by the electrocardiographic findings. The series of tracings presented cover a period extending from July 11, to July 18, 1932. Further studies were abruptly terminated by the patient's sudden death several hours after the last tracings had been recorded.

Figure 1 shows an auricular flutter with a ventricular rate of 40 and a constantly maintained auricular rate of 230 beats per minute, approximating roughly a 6:1 rhythm. There is a distinct shift of the axis to the left, with leads II and III exhibiting a downward direction of the QRS complexes. The QRS complexes are also slurred and splintered in the second and third leads.

In figure 2, taken two hours later, similar changes occur, except for an acceleration of the auricular rate to 430 beats per minute, the ventricular rate remaining the same as in figure 1. This was followed by another tracing three hours later, but it showed no appreciable changes.

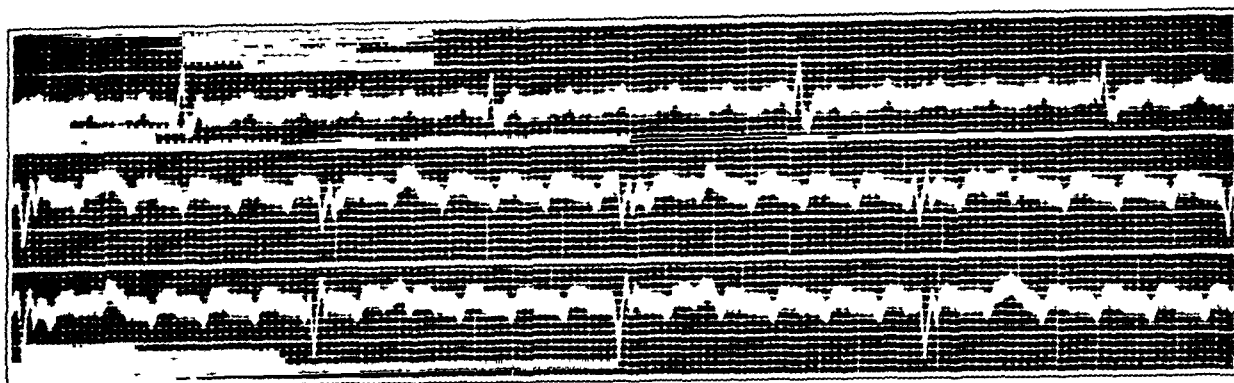


Fig 1—Auricular flutter with an approximate 6:1 rhythm

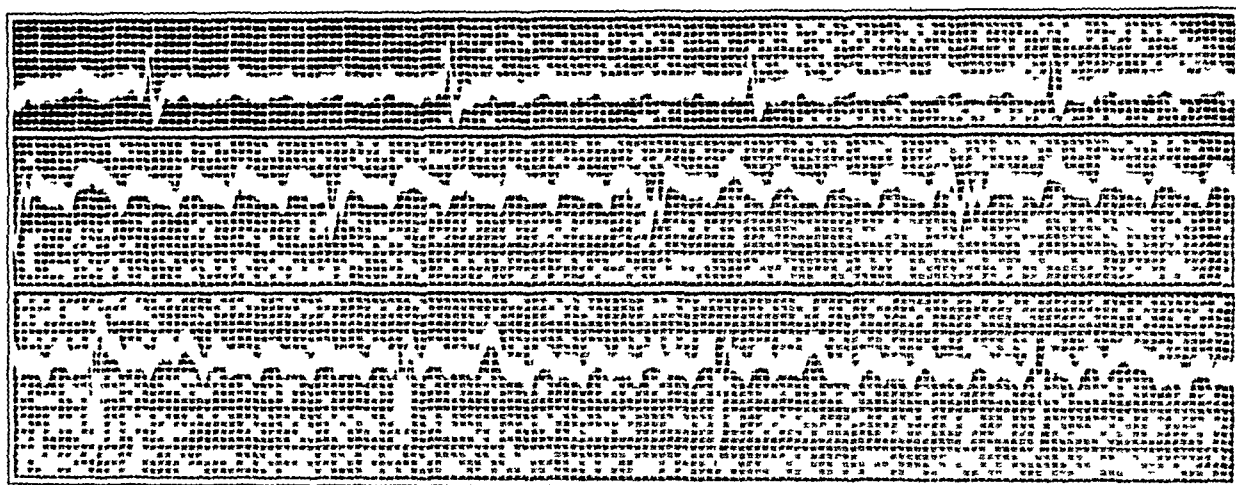


Fig 2—Same as figure 1, with an auricular rate of 430 beats per minute. Note the slow ventricular rate of 40

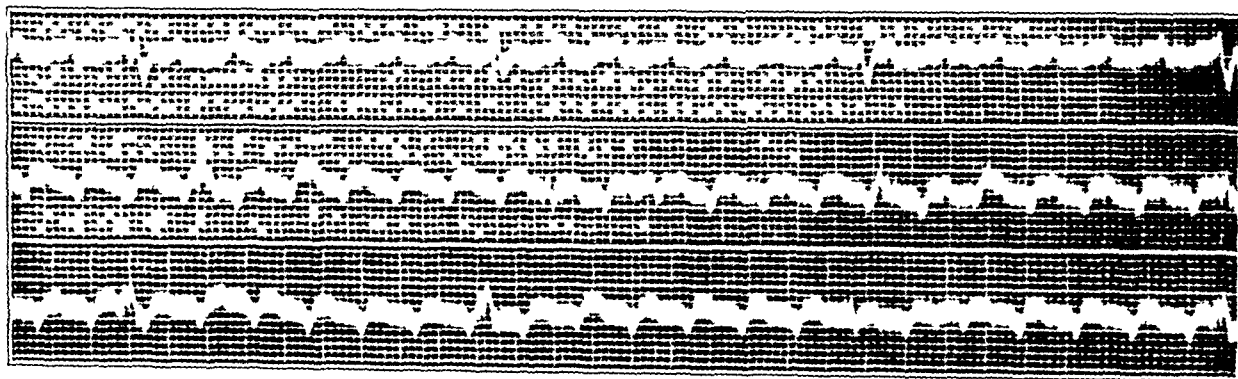


Fig 3—Shift of directional axis to the right

Figure 3, taken on the following day, exhibits a striking change in the directional axis, assuming now a definite right axial rotation. The auricular rate is again reduced to 230 beats per minute, while the ventricular rate remains unaltered.

Figure 4, taken two hours later, shows a change in contour of the various QRS complexes in lead I, some are directed upward, while others point definitely downward. The auricular rate in lead III is once more accelerated to 430 beats per minute.

To obtain a clearer conception in detail of the electrocardiographic findings, a double speed camera tracing was taken (fig 5). Here again we observe an unorthodox departure from the usual, the QRS complexes are directed upward in leads I and III, and downward in lead II. The uncommon auricular rate of 440 beats per minute is more clearly exhibited in lead III of this graph. There is no longer any doubt as to the rate of the auricular waves in this tracing, these are now clear and definite.

Between July 12 and July 18 the patient was much too ill for further electrocardiographic studies. Figure 6 was obtained on July 18 and shows a downward deflection of the QRS complexes in leads I and III, with an occasional QRS complex in lead III assuming an upward direction. Otherwise there are no spectacular changes.

Between this and the last tracing, the clinical picture of the patient became strikingly aggravated. The blood pressure no longer registered instrumentally, and complete cardiac collapse ensued. The patient suffered from extreme stenocardia with the pain radiating down both arms, he felt cold and clammy, perspired profusely and became much agitated and dyspneic. Figure 7, taken only a few hours before death, showed a right deviation of the electrical axis, the same rapid auricular rate in lead III previously noted, but in addition exhibited bizarre complexes following the QRS in leads II and III. These resemble in many respects the typical T wave alterations which have been described as occurring in coronary occlusion with infarction.

To facilitate the analysis of the seven electrocardiograms presented, we have graphically shown the various outstanding features of the tracings relating to the auricular and ventricular rates, the changes in axis deviation and the various alterations in the QRS complexes in the table.

The first description of auricular flutter we owe to MacWilliam,<sup>1</sup> who as early as in 1887 described such a rhythm after faradizing the auricles of dogs. This he appropriately designated as "auricular flutter." However, Ritchie,<sup>2</sup> in 1905, before the use of the electrocardiograph

1 MacWilliam, J. A. *J. Physiol.* 8:296, 1887.

2 Ritchie, W. T. Auricular Flutter with Complete Heart Block, *Proc. Roy. Soc. Edinburgh* 25:1085, 1905.

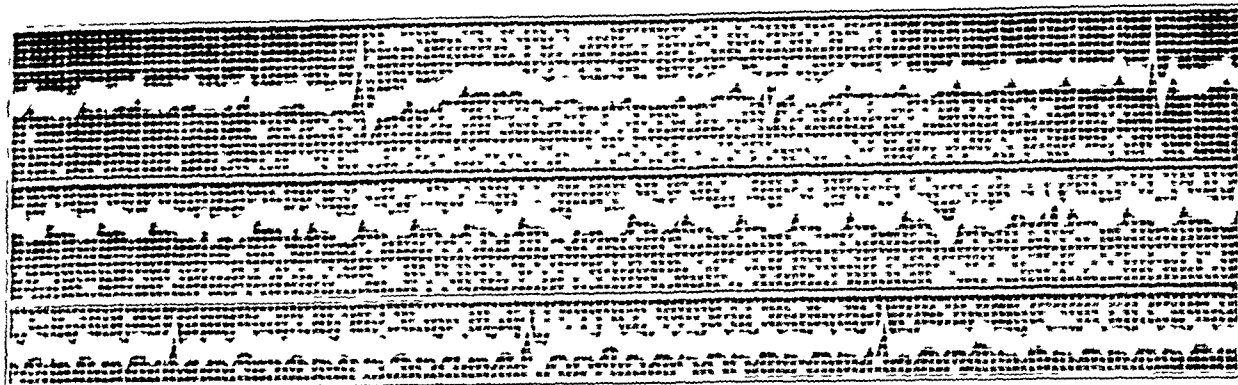


Fig 4—Note the directional changes of Q R S complexes in lead I

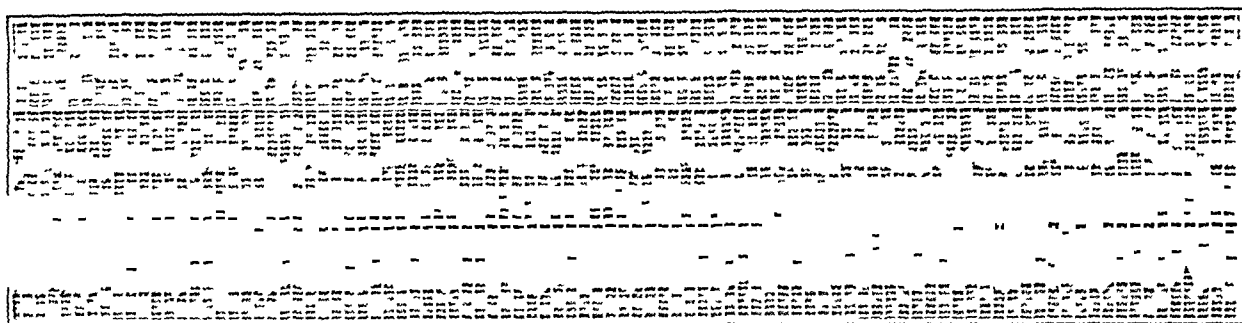


Fig 5—Tracing taken at double speed, rapid auricular rate clearly exhibited in lead III

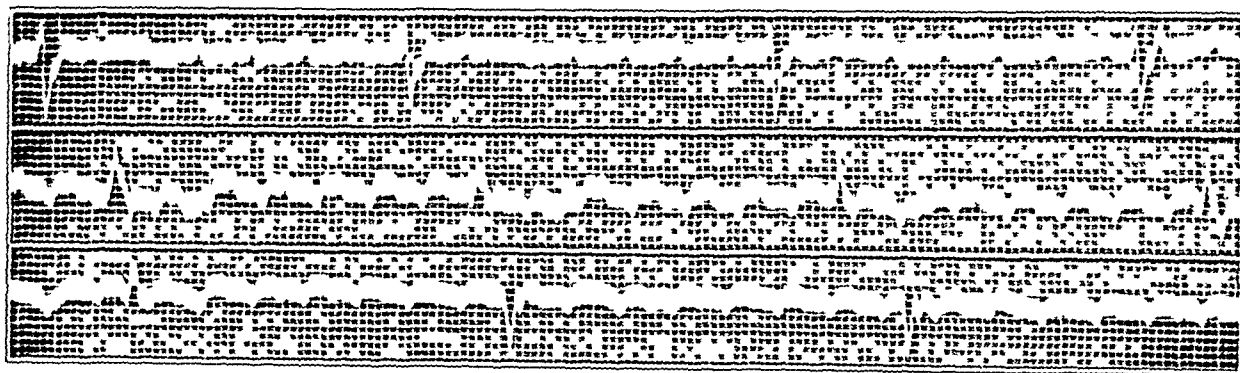


Fig 6—Undetermined axis deviation

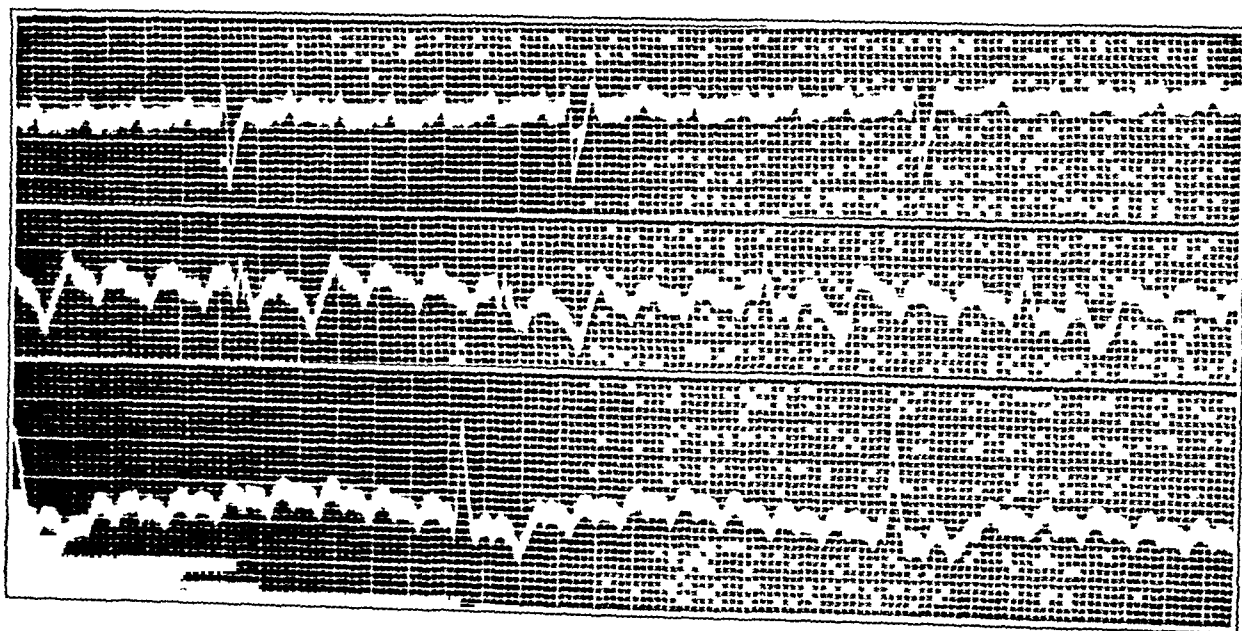


Fig 7—Leads II and III showing T wave changes usually associated with coronary occlusion with infraction



became general, was enabled to demonstrate polygraphically the presence of this abnormal rhythm because of the extreme slowness of the ventricular rate, which was unquestionably due to complete heart block. Four years later, the same author, in collaboration with Jolly,<sup>3</sup> again recorded the occurrence of auricular flutter with auriculoventricular dissociation electrocardiographically. Since that time only a few articles have appeared in the medical literature dealing with this rare combination of abnormal rhythms, these were by Hart,<sup>4</sup> De Boer,<sup>5</sup> Strauss,<sup>6</sup> Henderson and Rennie,<sup>7</sup> Roth,<sup>8</sup> Willius,<sup>9</sup> and Lian and Viau.<sup>10</sup> Roth,<sup>8</sup> in his book on "Cardiac Arrhythmias," dismisses this subject with a single tracing but no discussion. Willius,<sup>9b</sup> in 1929, reported only a single instance of auricular flutter with established complete heart block occurring in 168 cases of auricular flutter, observed on taking 40,000

*Analysis of Electrocardiograms Discussed*

Number of Tracing	Auricular Rate per Min	Ventricular Rate per Min	Axis Deviation	Q R S Interval, Sec	Additional Data*
1	230	40	Left	0 08	
2	230 to 420	40	Left	0 08	
3	230	40	Right	0 06 0 08	One Q R S complex in lead I directed upward
4	220 to 430	40	Undetermined	0 06 0 10	One Q R S directed downward and two Q R S's upward in lead I
5	220 to 440	40	None	0 08	
6	220	40	?	0 06 0 10	Q R S directed downward in leads I and III with one Q R S complex upward in lead III
7	220 to 440	40	Right	0 06 0 10	T waves characteristic of those found in coronary occlusion

\* Splintering of Q R S complexes occurs in all tracings

3 Jolly, W. A., and Ritchie, W. T. Auricular Flutter and Fibrillation, *Heart* **2** 177, 1909

4 Hart, T. S. Abnormal Myocardial Function, New York, The Rebman Company, 1917, p. 122, fig. 89, p. 125

5 De Boer, S. Auricular Flutter and Auricular Fibrillation in Total Heart Block, *Nederl tijdschr v geneesk* **1** 550, 1924

6 Strauss, A. E. Heart Block, Auricular Flutter and Adenoma of the Thyroid, *M. Clin. North America* **11** 487, 1927

7 Henderson, J., and Rennie, J. K. Auricular Flutter. A Case with Complete Heart Block, *Glasgow M. J.* **108** 355, 1927

8 Roth, I. Cardiac Arrhythmias, New York, Paul D. Hoeber, Inc., 1928, p. 201, fig. 71

9 Willius, F. A. (a) Auricular Flutter with Established Complete Heart Block, *Am. Heart J.* **2** 449, 1927, (b) Clinical Electrocardiograms, Philadelphia, W. B. Saunders Company, 1929, p. 62

10 Lian, C., and Viau, O. Electrocardiography of Auricular Flutter and Bradycardia Through Complete A-V Dissociation, *Arch. d. mal. de cœur* **23** 514, 1930

routine electrocardiograms. It is interesting to note in this connection that even in the most recent exhaustive treatise on heart disease by White,<sup>11</sup> only passing mention is made of this combination, further emphasizing its rarity.

It would not be amiss to point out that the controversy concerning the causative factors and mechanism instrumental in the production of auricular flutter has not been completely settled.<sup>12</sup> Although there are still some adherents to the theory that this rhythm is brought about by showers of auricular extrasystoles which are being initiated at such a rapid rate that the ventricles can no longer keep up with the accelerated rate from above, the majority of cardiologists today are in thorough accord with the circus movement theory of Lewis,<sup>13</sup> to which the authors unequivocally agree. From all standpoints, the latter seems to be by far the most plausible.

Of greater interest here is the unusual rapidity of the auricular rate which so closely approaches that seen in auricular fibrillation and yet maintains the perfect regularity and rhythmicity of flutter. If we are to allow that auricular fibrillation and flutter are both governed by the mechanism of circus movement, the ring of heart muscle about which the impulse circles in this particular case must of necessity be of a much smaller diameter than that existing in the usual types of flutter, yet large enough so that when the initial impulse reaches its starting point it finds the heart muscle just recovered from its refractory period. Thus, the circus remains unbroken and is enabled to continue.

Of interest also, as pointed out previously, is the rare combination of auricular flutter with complete heart block. The history of our patient makes us rather certain that complete auriculoventricular block preceded the development of auricular flutter by many years. The patient had mentioned the fact that as long as ten years ago he was refused life insurance because of a "slow pulse." Unfortunately, he was not specific enough as to the exact rate, his wife, however, volunteered the additional information that two years ago he had several spells of unconsciousness, this in the light of present knowledge may be suspected of fitting into the Stokes-Adams syndrome. Their occurrence antedated the complaint of fluttering sensations in the chest described in our patient's personal history. At best, it must be remembered that heart block is a much more common phenomenon than auricular flutter,

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11 White, P. D. *Heart Disease*, New York, The Macmillan Company, 1931.

12 Parsonnet, A. E. and Hyman, A. S. *Applied Electrocardiography*, New York, The Macmillan Company, 1929, p. 102. Hyman, A. S., and Parsonnet, A. E. *The Failing Heart of Middle Life*, Philadelphia, F. A. Davis Company, 1932, p. 312.

13 Lewis, T. *Graphic Registration of the Heart Beat*, London, Shaw & Sons, Ltd. 1925.

and also that auricular flutter seldom, if ever, is engrafted on a previously intact heart musculature. Hart,<sup>4</sup> in a discussion of the pathologic picture of auricular flutter, reports autopsy observations on three men of 51, 54 and 55 years of age, respectively, in each of whom little normal heart muscle could be found. They showed sclerosis of the coronary arteries with old infarcts invading the left ventricular walls. Another point that practically proves a preexisting damage to the heart muscle is the clearcut clinical picture of coronary occlusion with infarction which caused our patient's sudden death.

In a careful review of the literature we have been able to find but a single case with an auricular rate approaching in rapidity that exhibited in this report. It is the one reported by Hart,<sup>4</sup> as a 4:1 flutter with an auricular rate of 492 and a ventricular rate of 123, however this was not a case of complete heart block. We have also failed to note even a single instance of auricular flutter with coexisting complete auriculoventricular block occurring in a patient with an undoubted coronary occlusion with infarction, graphic evidence of which is seen in figure 7.

#### SUMMARY

A case of auricular flutter with an unusually high auricular rate is reported. This condition was superimposed over a complete dissociation of the auricles and ventricles in a patient who subsequently died with all the classic manifestations of coronary occlusion and infarction. Of singular interest is the rarity of such a combination of abnormal rhythms, the extremely high auricular rate, the rapid changes of axis in the various leads, the clear demonstration of flutter configuration in lead I and finally, the typical T waves as seen in coronary disturbances. The fact that few such cases have been reported in the literature has prompted us to publish this one.

# STANDARDIZATION OF CHEST LEADS AND THEIR VALUE IN CORONARY THROMBOSIS AND MYOCARDIAL DAMAGE

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AND

EVERETT DELONG, M.D.

LOS ANGELES

Interest in the use of chest leads in the diagnosis of coronary thrombosis was stimulated by Wolferth and Wood<sup>1</sup>. In a patient with normal standard leads with a clinical picture of coronary thrombosis, they found a striking abnormal deviation of the S-T interval from the isoelectric line in tracings taken with electrodes over the anterior and posterior surfaces of the chest. A second patient showed only a minor deviation from the normal in lead I and a more pronounced deviation in the chest lead, or lead IV. These changes they also found in experimentally produced occlusion of the coronary arteries<sup>2</sup>.

They state that "if conclusions are to be drawn from minor variations in the contour of the tracings in lead IV, the relation of electrodes to the heart should be kept constant. We paid no attention to minor variations in the position of the electrodes and have not drawn conclusions on these grounds." In our first attempts to take chest leads, we encountered marked rather than minor variations of the P, Q-R-S and T complexes in lead IV.

A few other observers personally stated that they had encountered the same difficulty. They, therefore, attempted to disparage the value of the chest lead.

We, accordingly, have attempted to standardize the curves obtained in chest leads by standardizing the position on the wall of the chest. We believe we have demonstrated the feasibility of obtaining uniform tracings by a standard technic. We present this technic in a series of one hundred and twenty-five normal control cases as well as in a series of clinical cases of coronary thrombosis and other forms of myocardial damage.

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From the Santa Fe Coast Lines Hospital, Los Angeles

1 Wolferth, C. C., and Wood, F. C. The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads. *Am J M Sc* **183** 30 (Jan.) 1932

2 Wood, F. C., and Wolferth, C. C. An Electrocardiographic Study of Experimental Coronary Occlusion. The Inadequacy of the Three Conventional Leads in Recording Certain Characteristic Changes in Action Current, *J Clin Investigation* **9** 815 (July) 1932

## NORMAL CONTROLS AND POSITIONS

As it has been demonstrated by Lewis and Wilson that changes in the position of the electrodes on the wall of the chest produce changes in the auricular-ventricular deflections of the electrocardiographic tracings, we have selected five positions for placing the electrodes. We feel that these five positions cover the anterior surface of the heart quite thoroughly, and are as follows:

Position A	Anterior	In the center of the chest at the level of the fifth to the sixth interspace
	Posterior	In the center of the back on the level with the anterior electrode
Position B	Anterior	Over the position of the maximum impulse of the heart
	Posterior	On the left side of the spine between it and the scapula at the level of the spine of the scapula
Position C	Anterior	On the left side of the chest over the second interspace about 2 to 3 inches from the midsternal line
	Posterior	Same as Position B
Position D	Anterior	Over the position of the maximum impulse
	Posterior	On the left side of the back below the angle of the scapula on the level with the anterior electrode
Position E	Anterior	In the center over the precordia
	Posterior	On the left side of the back on the level with the anterior electrode

Our first attempts to attain chest leads were by using the usual 4 by 6 inch arm electrodes placed over the precordia anteriorly and over the back posteriorly. The right arm wire goes to the anterior electrode and the left arm wire to the posterior electrode. We found considerable variation in the size and shape of the P, Q-R-S and T complexes. We then used a smaller, hollow, round copper cup, 2 inches in diameter, as suggested by the Sanborn Company. This was filled with a copper sponge "choreboy." These electrodes gave strikingly ununiform tracings when placed in various positions on the chest. The influence on the tracings of imperfect contact and lack of proper insulation was great. They gave results unreliable for clinical use.

Because of the consistently poor results with the foregoing electrodes, we have devised a new type. These we will describe briefly.

They consist of slightly concave circular copper plates, 2 and 4 inches in diameter. On the convex side is the terminal, situated in the center, welded to the plate at a right angle. Over the plate fits a flannel cloth which is held secure by a draw string. When one is ready to use it, the electrode is soaked in hot salt solution in the usual manner or contact made without the flannel cloths but with a special conducting paste.

It is important that the electrode be exceptionally well insulated, as this can be a great source of error and disturbance. Hard rubber is satisfactory. However, we would recommend that the steel spring clamp that holds the electrodes on to the chest have a bakelite mold on each end about 5 or 6 inches long. These will entirely insulate the electrodes from each other, as well as insulate the clamp from the body in case of accidental contact (fig 1).

We found that the 2 or 4 inch electrodes worked equally well with resistances under 1,000 ohms and gave curves which are practically identical. We believe that

the uniform results produced by this style of electrode are due to good insulation and good contact with the patient. They also are easy to make, inexpensive, and no trouble to use. They fit the chest snugly, owing to the slightly raised center, and are relatively trouble-free. Figure 2 illustrates the curves obtained in positions A, B, C, D and E by these electrodes on two normal subjects. It will be observed that the T wave is normally inverted. This is only an arbitrary matter and can be changed by reversing the lead wires to the machine. The interpretation of the tracings so far as the T wave is concerned is the reverse of that of the routine leads. Thus a normal chest lead has an inverted T, while the normal routine lead has an upright T. We have also confirmed the statement of Wilson<sup>3</sup> that the position of the posterior electrode bears no important influence on the shape of the chest lead. In fact, the posterior lead can be placed on either arm or leg and the same curve be obtained.

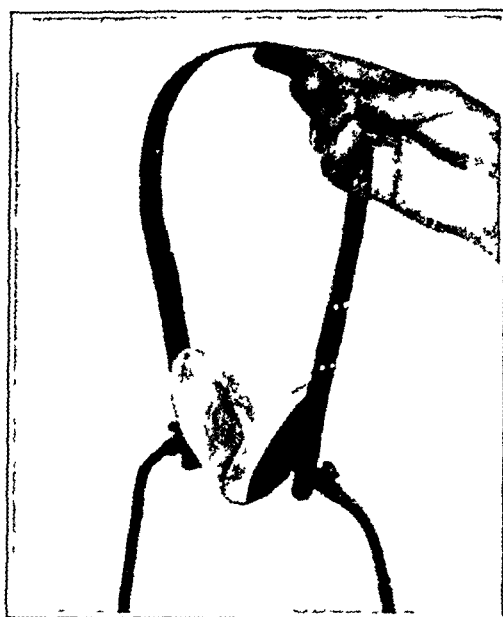


Fig 1—New type of chest electrodes with spring clamp to hold in position

#### COMMENT

It would be well to mention some of the fundamentals of the theory of electrocardiography in relation to the value of chest leads. The placing of the electrode on the arms and left leg and taking standard leads was by no means an arbitrary matter. Einthoven proposed the scheme of the equilateral triangle for the determination of the real direction of the potential difference in the heart and its manifest value, this being of value only on the frontal plane. The accuracy of the equilateral triangle was proved a short time later by Fahn, who showed that the variation of accuracy was within plus or minus 10 degrees. Wilson also proved this, showing that the galvanometer resistance produced no changes in the measurement of the potential difference.

<sup>3</sup> Wilson, F. N. The Distribution of Potential Produced by the Heart Beat Within the Border and at Its Surface, *Am Heart J* 5:599 (June) 1930.

At that time, it was mentioned by Fahr<sup>4</sup> that the frontal plane seemed sufficient for all practical purposes. This may still be true. However, there seems to be evidence that in some cases the use of other planes may be of value. Wolferth and Wood<sup>5</sup> demonstrated this in the recognition of abnormal chest leads in cases of coronary thrombosis in which the routine leads showed no abnormal changes.

The application of the equilateral triangle to the anteroposterior or to any plane other than the frontal is not possible. It has been shown by Wilson<sup>6</sup> that any sagittal plane varies with the body to such an extent that no definite geometric figure would bear practical relations as do the arms and leg to the frontal plane of the equilateral triangle.

It is evident that numerous planes present themselves for study. These planes all bear the relation of angle to the frontal plane. As yet, no way has been mentioned in the literature to determine the manifest

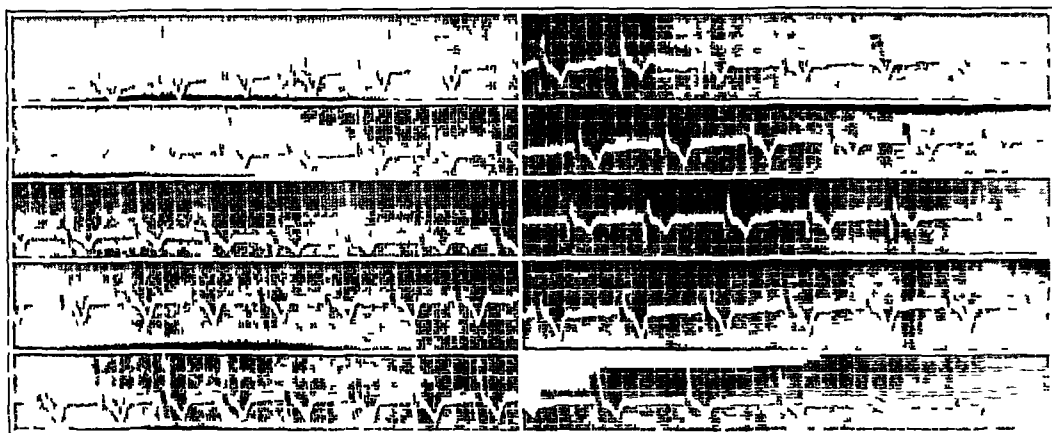


Fig 2—Chest leads in two normal subjects in positions A, B, C, D and E from above downward

value of the potential difference by leads taken in planes other than the frontal. We have chosen several anteroposterior planes from which to take tracings. These were confined to the center and the left side of the chest.

The location of the electrode on the chest is important in securing uniform tracings. The relatively slight changes discernible in the tracings on normal subjects in the various positions become markedly greater in the pathologic subjects, as will be shown. The diminution

4 Fahr, George. An analysis of the Spread of the Excitation Wave in the Human Ventricle, *Arch Int Med* **25** 146 (Feb) 1920

5 Wolferth, C C, and Wood, F C. Further Observations on the Use of Chest Lead in the Electrocardiographic Study of Coronary Occlusions, *M Clin North America* **16** 161 (July) 1932. Footnotes 1, 2 and 4

6 Wilson, F N, MacLeod, A G, and Barker, B S. The Potential Variation Produced by the Heart Beat Apices of Einthoven's Triangle, *Am Heart J* **7** 207 (Dec) 1931

in amplitude of the Q-R-S complex in position C as compared with the other positions is consistent with the location of the electrode over the base of the heart. This agrees with the fact pointed out by Wilson and Hermann<sup>7</sup> that the electrical effects of that part of the heart nearest the electrode will be exaggerated.

In the tracings from pathologic subjects, we found definite changes in only two positions, namely, positions A and B. Of these, B, over the position of the maximum impulse, was the more common. Because of

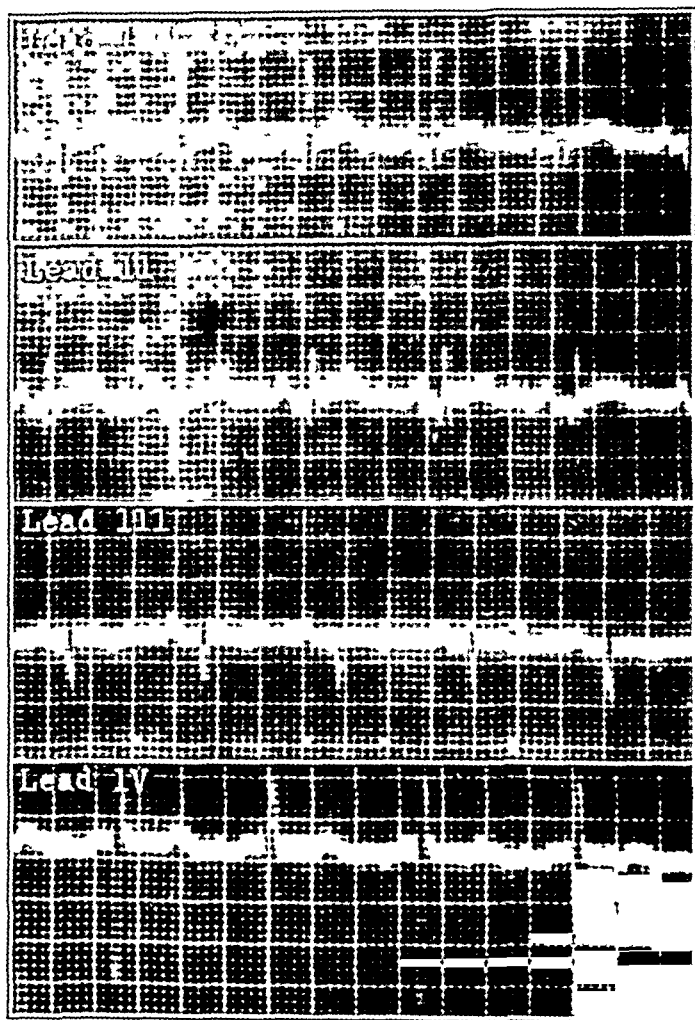


Fig 3 (case 1) —Chest leads on April 2, 1932

this, we recommended these two positions for use in cases in which it seems advisable. The possible value in localization of a myocardial infarct by means of change of position or size of electrodes is a problem for postmortem correlation. As yet, there are certain cases in which neither the standard leads nor the chest leads show any change. Our only explanation for this, as yet unproved, is the possible location of a small, infarcted area on the posterior surface of the heart.

<sup>7</sup> Wilson, F N, and Hermann, George. Bundle Branch Block and Arborization Block, *Arch Int Med* 26 153 (Aug) 1920



## REPORT OF PATHOLOGIC CASES

Our series of patients with thrombosis of the coronary artery on whom chest leads were taken falls into three groups (*a*) those showing normal standard leads and abnormal chest leads, (*b*) those showing abnormal standard as well as abnormal chest leads and (*c*) those showing abnormal standard leads but normal chest leads. A short summary of the clinical findings with the electrocardiographic tracings of these patients follows

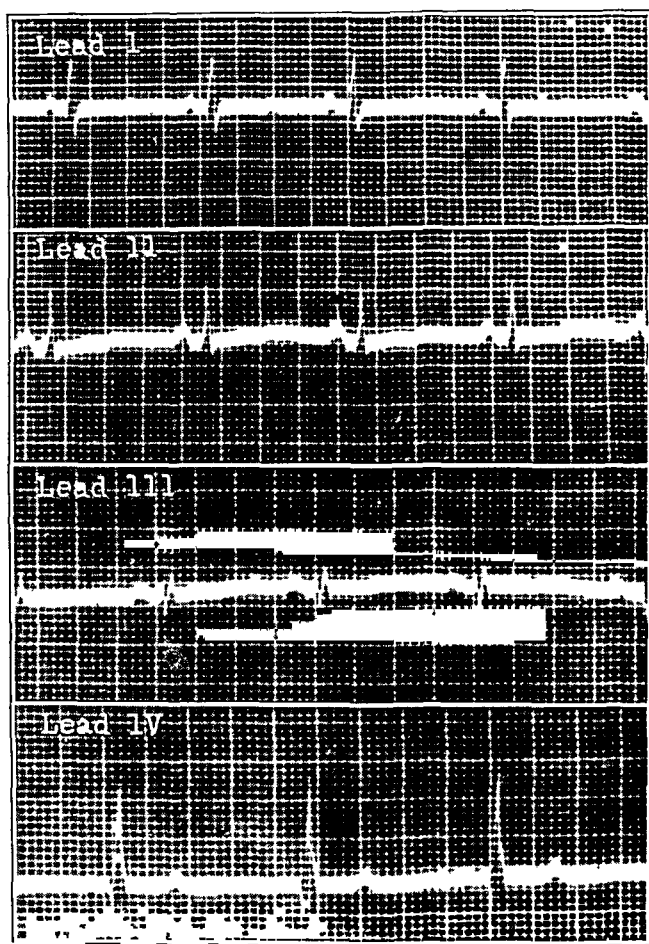


Fig 4 (case 2) —Chest leads on July 19, 1932

*Cases with Normal Standard Leads and Abnormal Chest Leads*—CASE 1—W T Q, a man, aged 66 years, an executive, entered the hospital on April 1, 1932, forty-eight hours after the onset of severe precordial pain radiating down both arms and accompanied by dyspnea. The temperature was 102 F, the pulse rate, 110, the blood pressure, 104 systolic and 72 diastolic, and the white blood cells, 8,500. A tracing taken on April 2 (fig 3) showed practically normal standard leads with a definitely upright T in lead IV taken in position B. In all tracings hereafter, if not otherwise mentioned, lead IV is represented as taken in position B. In all of these instances, the T wave in position A was normal. However, whenever position A revealed an abnormality it was reproduced beneath

position B Ten days later, April 12, there had developed a definite inversion with the coving of  $T_1$  and  $T_2$  with a high take-off in lead II In the chest lead, the T wave was iso-electric On April 27, the findings were essentially the same except for a slightly inverted T in lead IV On July 23, a diminution in the negativity of  $T_1$  and  $T_2$  was exhibited On August 8, there was only a slightly inverted  $T_1$  and iso-electric  $T_2$  with the T in lead IV, position B, definitely inverted but not to a normal degree On September 1, a further progression to normal of the T wave in lead IV was seen

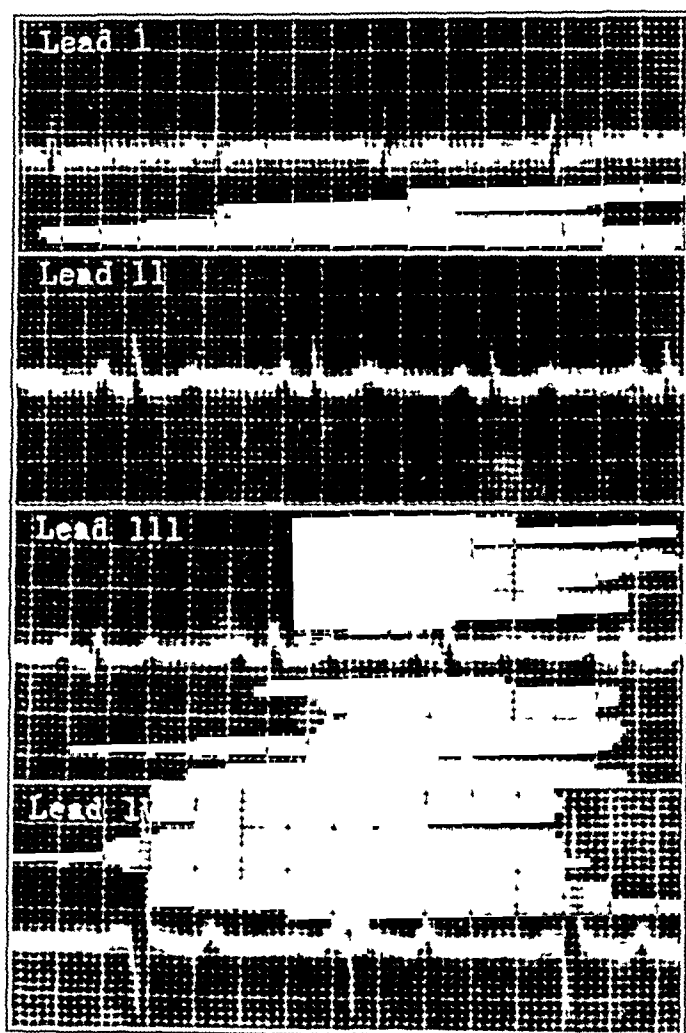


Fig 5 (case 3) —Chest leads on May 19, 1932

Owing to lack of space and prohibitive cost of reproduction, only the first tracing of this patient is presented All subsequent tracings are therefore described in the text only For the foregoing reasons, in the remainder of the following case reports, only one characteristic abnormal electrocardiograph is reproduced, and the subsequent return to normal is described without reproduction of the tracings

CASE 2—M S, aged 47, a housewife, entered the hospital on May 13, 1932, with the complaint of precordial pressure following exertion attendant on a fright in the mountains eight days previously The temperature was 99 F, the pulse rate, 100, the blood pressure, 112 systolic and 70 diastolic, and the whole blood

cells, 10,800 An electrocardiogram taken on admission showed a slightly low take-off and coving with inversion of  $T_2$  and  $T_3$ . Four days later, on May 17, there was an upright  $T_1$  and iso-electric  $T_3$ . The chest lead, however, revealed a distinctly abnormal upright T wave. This remained the same on May 28, June 11, July 1 and July 19, when the patient was discharged from the hospital improved. The tracing of July 19 is reproduced (fig 4)

CASE 3—G B, aged 61, a section foreman, was first seen on Oct 16, 1930, several days after an attack of severe substernal pain and pressure. This was so

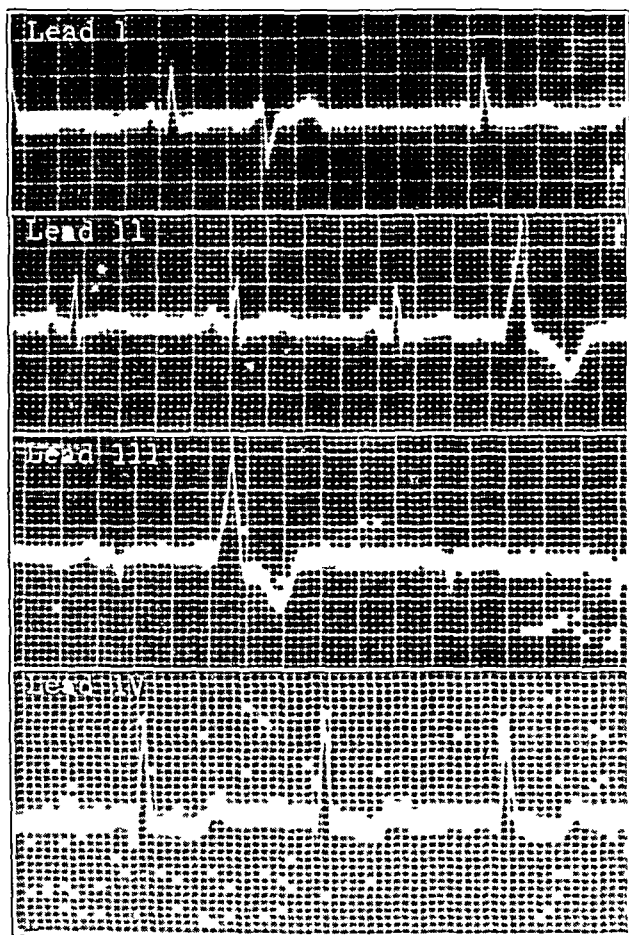


Fig 6 (case 4) —Chest leads on May 22, 1932

severe he had to lie down for relief. The pain persisted and radiated down the left arm. The temperature was 100 F, the pulse rate, 98 and the white blood cells, 10,300. An electrocardiogram at this time revealed a high take-off of  $T_1$  and marked inversion of  $T_1$  and  $T_2$ . Recovery was uneventful. He returned on May 19, 1932, with evidence of mild congestive failure, and an electrocardiogram taken on that date (fig 5) revealed marked slurring of the Q-R-S complex in leads II and III with upright T waves throughout. The chest lead, however, demonstrated a markedly abnormal upright T wave. By June 21, he had developed a complete auricular-ventricular dissociation with a ventricular rate of 50 and also marked slurring of all the Q-R-S complexes. The T wave in lead IV was slightly inverted. On August 30, the complete dissociation had ceased, but a

prolonged P-R interval of 0.24 second was present. The T wave in lead IV in the meantime had become more inverted and was practically normal.

CASE 4—W. B., aged 63, a locomotive engineer, entered the hospital on July 27, 1931, with a story of pain in the anterior portion of the chest radiating down the left arm and brought on by exertion. An electrocardiogram on July 28 showed a practically normal tracing. The patient was discharged with a diagnosis of angina pectoris but reentered the hospital on November 26, after three days of agonizing pain in the chest accompanied by dyspnea. The temperature was 100 F., the pulse rate, 110, the blood pressure 130 systolic and 86 diastolic, and the white

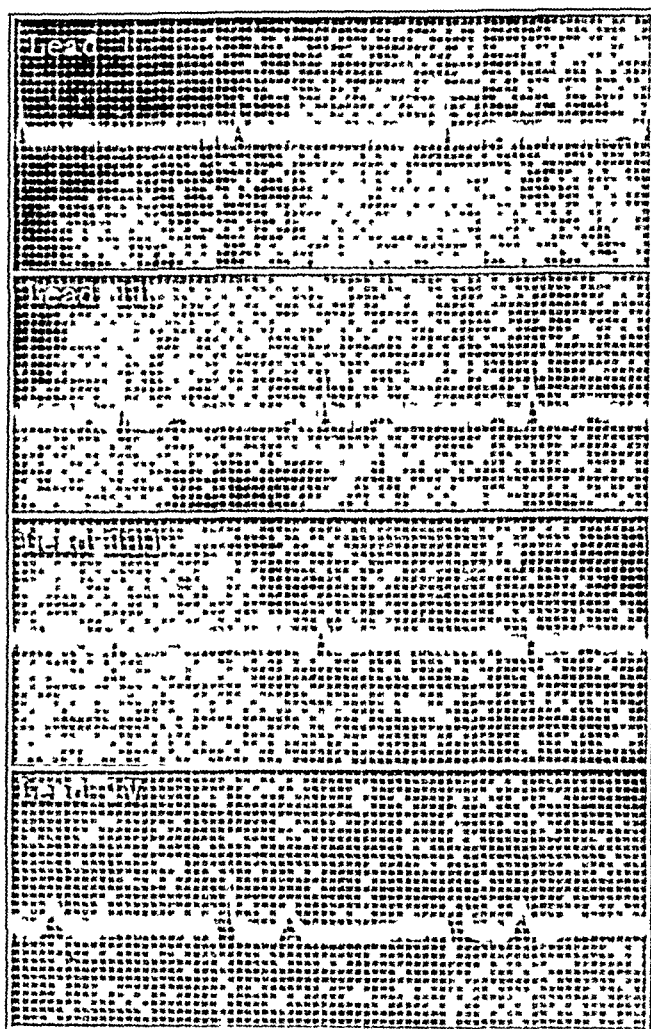


Fig. 7 (case 5)—Chest leads on July 18, 1932

blood cells, 11,100. An electrocardiogram taken on that date revealed a marked change in  $T_1$  and  $T_2$  which were definitely coved and inverted. On May 22, the patient was recalled for examination, and an electrocardiogram (fig. 6) showed a return to practically normal standard leads with frequent premature ventricular contractions. The first chest lead on this patient taken at this time revealed a markedly abnormal upright T wave, indicating the probable value of the chest lead in demonstrating residual damage months after the standard leads had returned to normal.

CASE 5—W. V., aged 53, a yard clerk, was seen on Nov. 11, 1930, for recurrent attacks of substernal pain with dyspnea and inability to work. The blood

pressure was 150 systolic and 100 diastolic. An electrocardiogram taken then showed low voltage of all Q-R-S complexes with slight slurring of Q-R-S in leads II and III and an iso-electric  $T_1$ . On April 18, following an attack clinically simulating coronary thrombosis, an electrocardiograph revealed only slurring of Q-R-S<sub>2</sub> and Q-R-S<sub>3</sub>. On May 19, all Q-R-S complexes were slurred, and the T wave in lead IV was abnormal, in that it was of small amplitude although slightly inverted. On July 18 (fig 7), there was less notching of the Q-R-S complexes, but the T wave in lead IV was markedly upright.

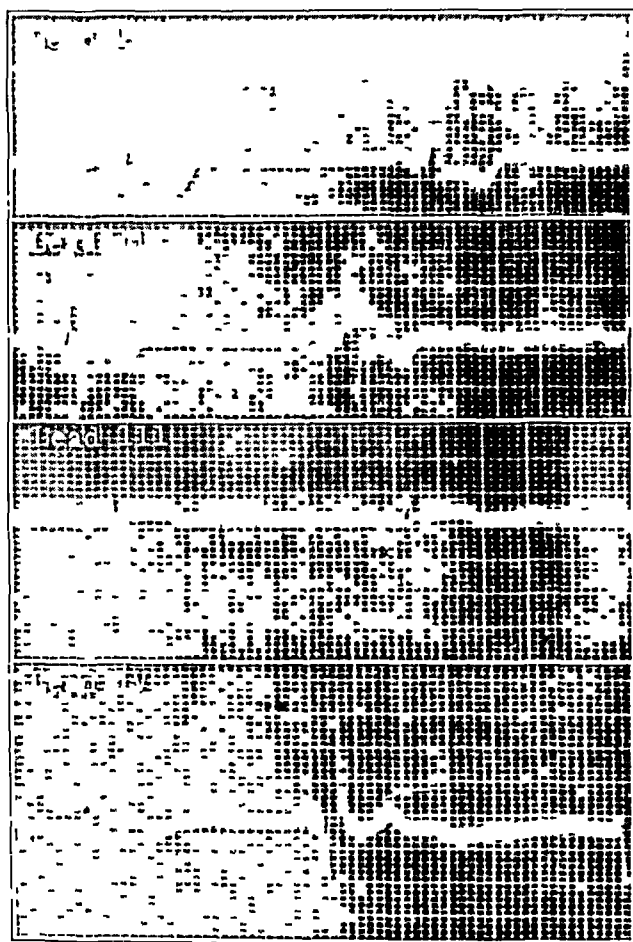


Fig 8 (case 6) —Chest leads on June 11, 1932

*Coronary Cases with Both Abnormal Standard and Chest Leads*—CASE 6—J W, aged 57, a section foreman, entered the hospital first on Aug 4, 1931, following a severe attack of precordial pain lasting eight days. The temperature was 98 F, the pulse rate, 80, the blood pressure, 234 systolic and 140 diastolic, and the white blood cells, 9,200. An electrocardiogram taken on that date revealed a definite inversion with low take-off of  $T_1$  and  $T_2$  and left ventricular preponderance. The patient was discharged on August 28, but reentered the hospital on May 20, 1932. An electrocardiogram taken the following day revealed  $T_1$  still inverted, but  $T_2$  iso-electric. The T in lead IV was abnormally diphasic. On June 11 (fig 8), the T wave in lead IV was upright and remained so until the patient's death from uremia on July 17.

Autopsy revealed marked general arteriosclerosis, primary contracted granular kidneys and an old thrombosis of the descending branch of the left coronary artery. A myocardial infarct, 2 by 3 cm, was present on the anterior surface of the left ventricle near the apex directly on the anterior surface of the heart. This patient was the only one in our series of coronary cases who died and on whom we could perform an autopsy to confirm the presence of a coronary thrombosis to correlate with the electrocardiographic changes found in life.

CASE 7—W. G., aged 63, a railroad conductor, was first seen on May 5, 1932, in the midst of an attack of gripping pain in the chest. This had been present two

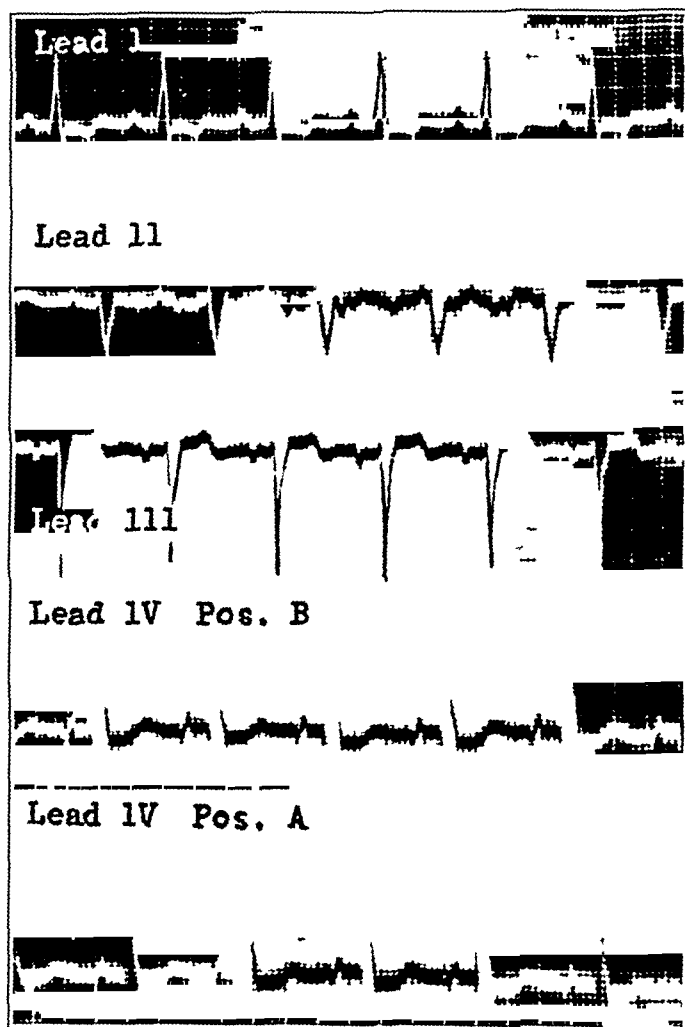


Fig 9 (case 7) —Chest leads on May 13, 1932

days. The temperature was 100.4 F, the pulse rate, 96, the white blood cells, 9,700 and the blood pressure, 136 diastolic and 90 systolic. Evidences of mild congestive failure were present. An electrocardiogram taken on May 7, revealed an upright T wave in lead IV in both positions B and A. The T wave in lead I was inverted, and there was moderate spreading of the Q-R-S complexes in all of the three standard leads. On May 13 (fig 9), the findings were virtually the same. During June and July, the T wave in position A gradually resumed its normal contour, with the T wave in position B becoming first diphasic and then slightly inverted. On August 1 (fig 10), the T waves in both positions returned to normal and have remained so to date.

CASE 8—H K, aged 58, an inspector, entered the hospital on May 27, 1932. Fifteen days before admission he had severe knifelike pain over the precordia lasting several hours and radiating down the left arm. He had been dyspneic on slight exertion since. The temperature was 98.6 F, the pulse rate, 90, the blood pressure, 184 systolic and 100 diastolic, and the white blood cells, 7,100. An electrocardiograph taken on May 28 (fig 11), revealed an inverted T in lead I and abnormal T waves in position A and B of the chest lead. On June 22, a return of the inversion of  $T_1$  to upright and an inversion of  $T_2$  and  $T_3$  was demonstrated. However, in the chest leads in both position, the T waves were

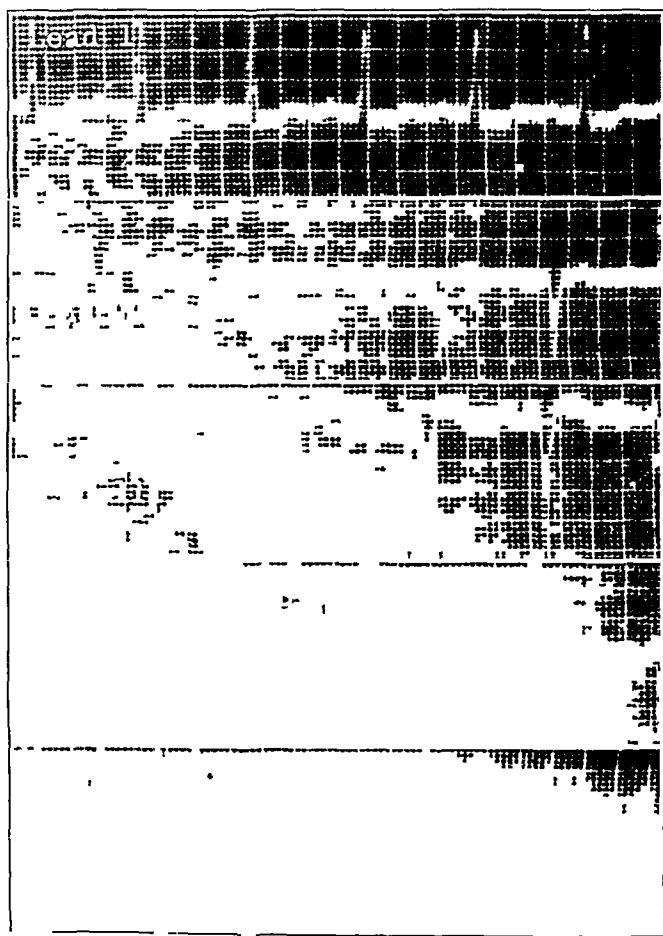


Fig 10 (case 7)—Chest leads on Aug 1, 1932

normal. On September 21, the inversion of  $T_2$  and  $T_3$  had disappeared. The chest lead remained normal.

CASE 9—V T, aged 34, a rotary worker, entered the hospital on April 25, 1932, following an attack of severe precordial pain lasting one-half day and followed by persistent dyspnea. The temperature was 100.4 F, the pulse rate, 100, the white blood cells, 14,400, and the blood pressure, 120 systolic and 70 diastolic, and later 110 systolic and 80 diastolic. An electrocardiogram taken on April 30, demonstrated an inversion of T in leads II and III with an only slightly abnormal T in lead IV. The patient was released to his home for convalescence on May 18, and within two days suffered an excruciating pain in the chest which lasted no less than nine days. He required morphine many times

daily for relief. An orthodiagram revealed a marked hypertrophy of the heart. He was seen by several consultants who concurred in the diagnosis of coronary thrombosis. An electrocardiogram taken on May 28, revealed an inverted  $T_1$  with a bigeminy due to frequent nodal extrasystoles. The T wave in lead IV was diphasic. On July 18, the T waves were largely iso-electric, and the T wave in lead IV was upright. Tracings made on August 24 and September 13, demonstrated a gradual return to normal of lead IV. These tracings are not reproduced.

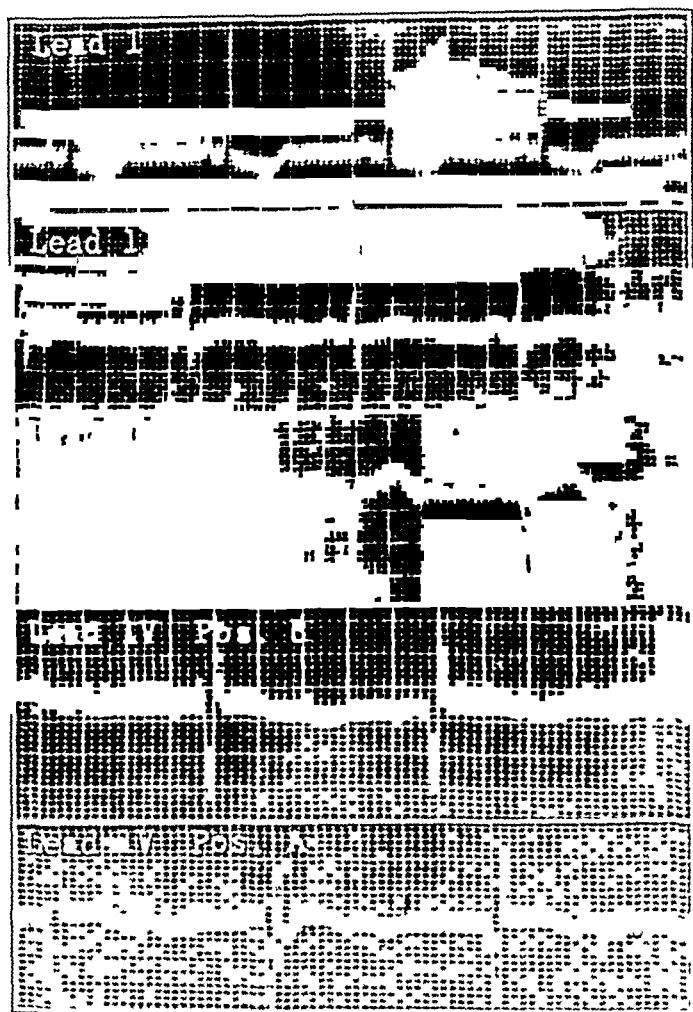


Fig. 11 (case 8) —Chest leads on May 28, 1932

CASE 10—W. S., aged 58, a brakeman, was sent into the hospital on Oct. 4, 1932, for re-checking because of a known old hypertension. He had no complaints. Eighteen months prior to admission he had had an attack of precordial pain which lasted several hours and required morphine for relief. There had been no return of pain in the chest, and he stated he was rarely short of breath. The blood pressure was 210 systolic and 100 diastolic. An electrocardiogram, taken on October 8, revealed an inversion of  $T_1$  and  $T_2$  with the T wave in lead IV, position B, diphasic but normal in position A. This tracing is not reproduced.

*Coronary Cases with Abnormal Standard Leads and Normal Chest Leads—*

CASE 11—L. R., aged 57, a pumper, entered the hospital on April 25, 1932, with a history of a severe attack of pain in the chest on April 13, lasting eight hours. He was having persistent dyspnea. The temperature was 98.6 F, the pulse rate,



80, and the white blood cells, 5,200. An electrocardiogram taken on April 28, demonstrated an inverted  $T_2$  and  $T_3$  with left ventricular preponderance. On May 11, these findings still persisted. A chest lead on this date was entirely normal. The patient's dyspnea has persisted. A re-check on the chest lead subsequently showed no change. The tracings are not reproduced as they showed a normal lead IV.

CASE 12—J W, aged 45 years, a carpenter, was seen on July 7, 1932, following severe substernal pain of agonizing character. Syncope accompanied this distress. The temperature was 100.6 F, the pulse rate, 110, the white blood cells, 19,000, and

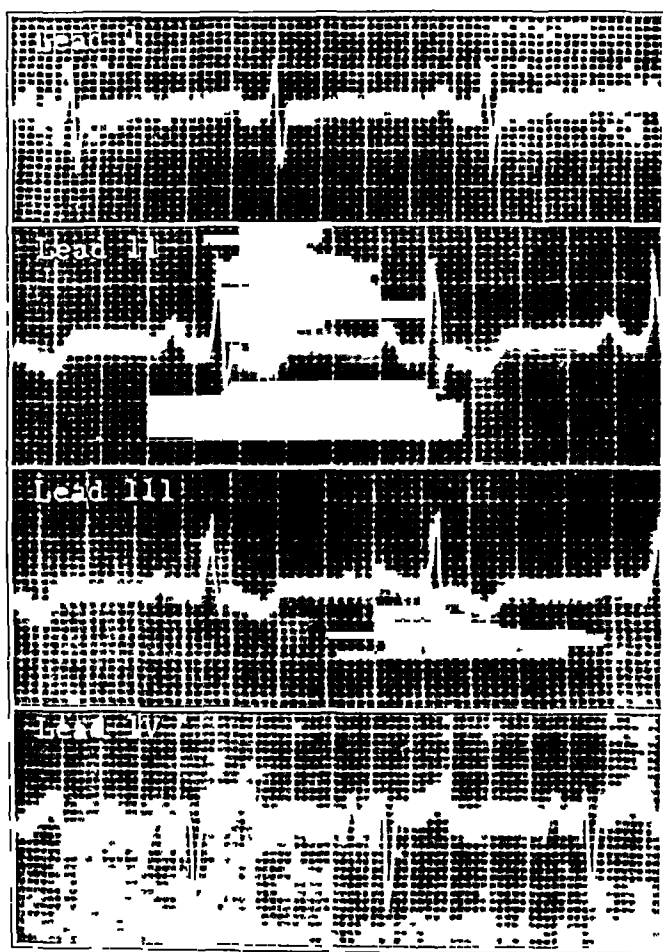


Fig 12 (case 14)—Chest leads on June 11, 1932

the blood pressure, 92 systolic and 65 diastolic, later, 104 systolic and 55 diastolic. An electrocardiogram taken on July 9, and one on July 19, revealed a markedly inverted  $T_2$  and  $T_3$  which had a high take-off on the earlier date. The patient was discharged after two months and recalled for a chest lead on May 25. On this date, his  $T_2$  was iso-electric and the  $T_3$  had remained inverted. The T wave in lead IV, however, was normal. These tracings are not reproduced.

CASE 13—H E, aged 72, a crossing watchman, entered the hospital on Jan 11, 1930, for prostatic obstruction. The electrocardiograph was normal. The first stage was done on January 17, and the second stage on March 6. The patient was convalescing satisfactorily, when on April 10, while walking in the ward, he

was seized with a terrific precordial pain and fell to the floor. He was in partial shock for some hours. The temperature was 99 F, the pulse rate, 106, the blood pressure, 96 systolic and 70 diastolic, and the white blood cells, 11,000. A series of three electrocardiograms on April 12, 16 and July 29 revealed progressive changes characteristic of thrombosis of the coronary artery. The patient recovered and has been moderately active since. He was recalled on June 3, 1932, for re-checking, his standard leads revealed a residual marked inversion of  $T_2$  and  $T_3$ , but a normal chest lead. His tracings being normal in lead IV, they are not reproduced.

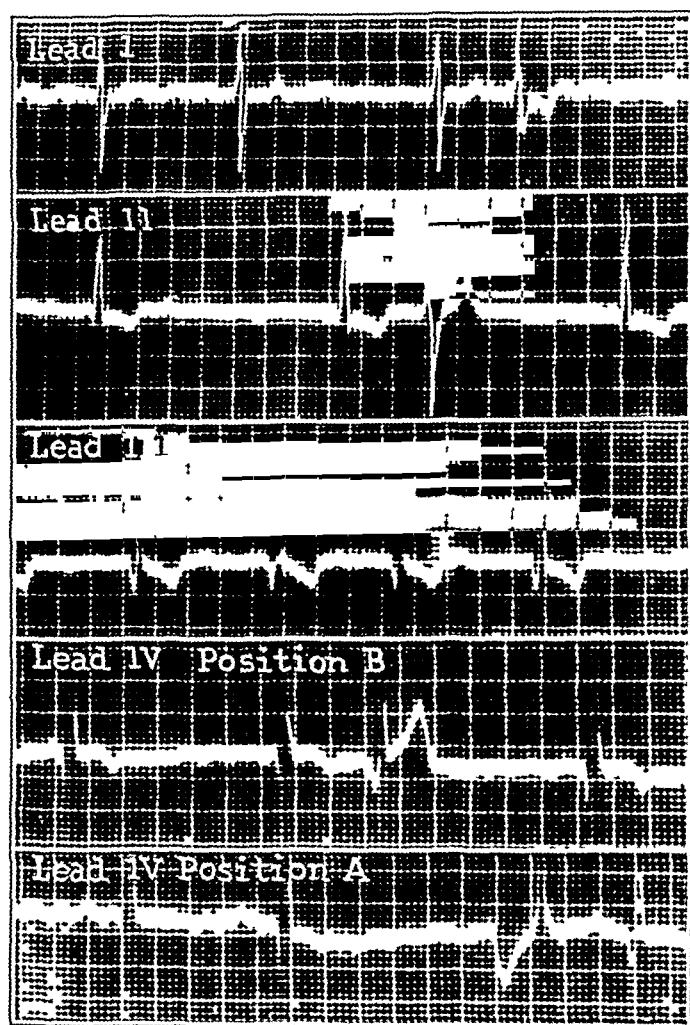


Fig 13 (case 15) —Chest leads on June 11, 1932

*Chest Leads in Forms of Myocardial Damage other than Coronary Thrombosis*—CASE 14—J B, a woman, aged 47, a secretary, had been a known sufferer from rheumatic endocarditis with mitral stenosis for over five years. She had always had a regular sinus rhythm. Her first break in compensation occurred on Nov 6, 1930. An electrocardiogram taken on that date revealed only a diphasic  $T_1$ . On March 3, 1931, an inversion of  $T_2$  and  $T_3$  was present. The patient was fully digitalized at this time. On June 11 (fig 12), these findings were still present. The T wave in lead IV was highly abnormally upright. The P wave was also upright. These findings were checked on three occasions.

In view of the occasionally reported instances of coronary occlusion in rheumatic pancarditis, we were anxious to check the observations on this patient

post mortem She died of progressive congestive failure on Sept 24, 1932 Autopsy by Dr E V Hall of the University of Southern California Medical School demonstrated a contracted, stenosed, "fish mouth" mitral valve There was no evidence of pericarditis The coronary arteries were patent throughout There was no gross area of myocardial fibrosis, although microscopically Aschoff bodies and fibrosis were found

These findings demonstrate that the T wave changes in lead IV are not solely due to infarction of the myocardium resulting from coronary

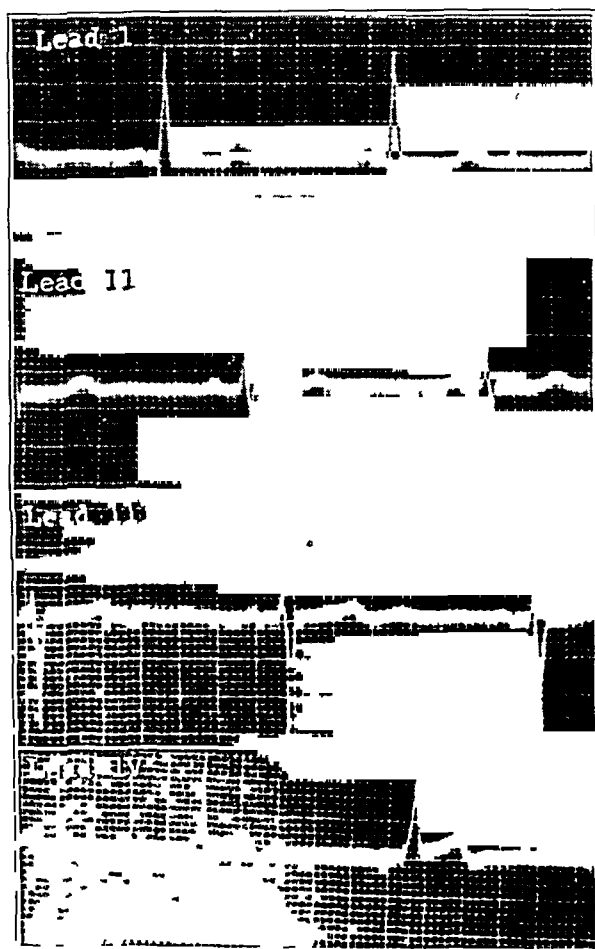


Fig 14 (case 16) —Chest leads on July 19, 1932

thrombosis The character of the inversion of  $T_2$  and  $T_3$  is suggestive of a digitalis effect However, it is highly unlikely that the T in lead IV can be made upright by digitalis At least, we have seen no such cases The patients in cases 1, 2, 3 and 4 all showed upright T in lead IV and received no digitalis whatever

CASE 15—G M, aged 36, a laborer, had been followed from 1926 for a rheumatic endocarditis with mitral stenosis and insufficiency In that time, he had suffered five attacks of decompensation He maintained a regular sinus rhythm until the onset of an auricular fibrillation early in June 1932 An electro-

cardiogram taken on Oct 30, 1929, revealed a diphasic T wave in leads II and III. On May 25, 1932  $T_2$  and  $T_3$  were inverted. On June 11 (fig 13), an electrocardiogram revealed the same findings with auricular fibrillation. The chest leads in positions A and B revealed a slightly inverted T in position B and an iso-electric T in position A.

The patient died on October 4, and autopsy revealed a marked mitral stenosis, moderate involvement of the aortic valve and considerable adhesive pericarditis. The coronary arteries were normal. Microscopically, much fibrosis and Aschoff bodies were found.

CASE 16—A C, aged 45, a laborer, was admitted to the hospital on July 19, 1932, because of swelling of the abdomen and weakness. Examination revealed a markedly enlarged irregular liver, ascites and edema of the legs. The Wassermann reaction was four plus. An orthodiagram revealed a hypertrophied heart and a uniformly widened aortic arch. There were no murmurs. The heart rate was regular. An electrocardiogram taken on July 19 (fig 14) demonstrated normal standard leads but an abnormal lead IV with an upright T wave. This was checked on several occasions before death and remained unchanged. The patient died of massive hematemesis on September 24.

Autopsy revealed a primary carcinoma of the liver engrafted on an old cirrhosis of the liver. Advanced syphilitic aortitis was present. The heart was hypertrophied but free from valvular defects, with normal coronary arteries. Microscopically, considerable fibrosis of the myocardium was present.

This was the only patient in our series without coronary disease with a normal electrocardiogram in regard to standard leads and an abnormal chest lead.

We have taken chest leads on six patients with advanced bundle branch block, in all of whom lead IV was normal except for widening of the Q-R-S complex. In a series of several hypertensive patients, all with normal standard electrocardiograms, no abnormalities in the chest leads were discovered. One patient with congenital heart disease presented similar findings. Tracings of these patients are not reproduced.

#### CONCLUSIONS

From the foregoing study, we feel we are justified in the following conclusions concerning chest leads. By uniform technic, with care as to the position of the electrodes, uniformly normal tracings can be secured on patients with normal hearts. In no instances did we obtain other results, and only in diseased hearts did we obtain abnormal chest leads. The changes found in diseased hearts were not limited to patients with coronary thrombosis. However, they were found most frequently in patients with this affliction. These changes occurred in such patients in whom standard leads were either normal or abnormal. Occasionally apparently the lead IV changes occurred before abnormalities arose in the standard leads. Frequently they reverted to normal before the standard lead abnormalities had done so. In a few instances, they remained for many months presumably as evidence of residual myocardial damage long after the standard leads had become normal.

In a small group with characteristic changes of coronary thrombosis in the standard leads, no abnormalities in the chest lead were noted

Abnormal chest leads were found in two instances of rheumatic heart disease with mitral stenosis—both with abnormal standard leads—and in one patient with syphilitic heart disease. The latter had normal standard leads. None of these patients had evidence of coronary disease post mortem. One of the rheumatic hearts had considerable adhesive pericarditis

#### SUMMARY

- 1 A standard technic for obtaining chest leads is presented
- 2 The position of the electrode on the chest is of importance. Uniform tracings can be secured in normal patients by this technic. In diseased hearts, two positions may show abnormal chest leads. Usually, however, only one of these positions shows such an abnormality. When present in both positions, one may revert to normal earlier than the other
- 3 The changes found are not specific for coronary thrombosis, for they were found in other types of myocardial damage confirmed by autopsy
- 4 In patients with coronary thrombosis, however, a relatively characteristic chest lead deformity is noticed. Besides Wolferth's and Woods S-T deformity, we found a more frequent abnormality of an iso-electric or upright T wave in lead IV
- 5 These T wave abnormalities in the chest lead occasionally precede changes in the standard leads and are, therefore, of value in an earlier confirmation of a diagnosis of coronary thrombosis. They also occur in instances in which the standard leads show the characteristic abnormalities of coronary thrombosis. In some cases of this type, the lead IV changes may be absent
- 6 The chest lead abnormalities change with improvement in the patient's condition, implying that an acute underlying process is taking place. Occasionally a return to normal occurs in the chest lead but not in the standard leads. The reverse of this appears to occur even more frequently
- 7 As pathologic changes which occur in the myocardium are not all recorded in either the chest leads or the routine leads alone, we feel that it is a worth while procedure to run the chest leads in all cases of suspected or proved myocardial damage. In all the patients on whom we took such tracings, in whom there was clinical evidence of heart disease, either the chest lead or the routine leads showed evidence of myocardial damage. In none of these patients did we find both the routine and the chest leads normal

Photographs were supplied through the courtesy of Dr. E. L. Shultz and Dale L. Smith, superintendent of the Santa Fe Hospital, and Miss Maureen Springsteen, R. N., gave invaluable technical assistance

# ELECTROCARDIOGRAPHIC STUDIES OF THE DYING HUMAN HEART

WITH OBSERVATIONS ON THE INTRACARDIAC INJECTION OF  
EPINEPHRINE, REPORT OF TWENTY-FIVE CASES

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W K PURKS, M D

AND

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Electrocardiography has increased our knowledge of the human heart in health and disease. Its usefulness does not end here, for we may proceed further and investigate the heart in the last moments of life and even after life has apparently ceased. The phenomena of clinical death, as manifested by the cessation of respiration and audible heart sounds, have been observed repeatedly. That cardiac activity does not cease simultaneously with clinical death and that, in certain instances, it continues for a prolonged period is best revealed by the electrocardiograph.

Since the original work of Rhomer<sup>1</sup> in 1911, various observers<sup>2</sup> have described the sequence of events occurring in electrocardiograms taken during the last moments of life. Turner,<sup>3</sup> in a recent review of the literature, collected sixty-five cases in which electrocardiograms

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From the Department of Medicine, Emory University Medical School, and the Emory Division of Grady Hospital.

1 Rhomer. *Munchen med Wchnschr* **58** 2358, 1911.

2 Robinson, G C. A Study with the Electrocardiograph of the Mode of Death of the Human Heart, *J Exper Med* **16** 291, 1912. Halsey, R H. A Case of Ventricular Fibrillation, *Heart* **6** 67, 1915. Dieuaide, F R, and Davidson, E C. Terminal Cardiac Arrhythmias. Report of Three Cases, *Arch Int Med* **28** 663 (Nov.) 1921. Schellong, F. Elektrokardiographische Beobachtungen am sterbenden Menschen, *Ztschr f d ges exper Med* **36** 297, 1923. Willius, F A. Changes in the Mechanism of the Human Heart Preceding and During Death, *M J & Rec* **119** 49, 1924. Reid, W D. Ventricular Ectopic Tachycardia Complicating Digitalis Therapy, *Arch Int Med* **33** 23 (Jan.) 1924. Kahn, M H, and Goldstein, I. The Human Dying Heart, *Am J M Sc* **168** 388, 1924. Martini, P, and Skell, J. Das Sterben des menschlichen Herzens, *Deutsches Arch f klin Med* **158** 350, 1928. Willius, F A. *Clinical Electrocardiograms*, Philadelphia, W B Saunders Company, 1929. von Hoesslin, quoted in Berlin letter, *J A M A* **96** 786 (March 7) 1931.

3 Turner, K B. The Mechanism of Death of the Human Heart as Recorded in the Electrocardiogram, *Am Heart J* **6** 743, 1931.

were taken during death. To this series he added five cases. We are reporting in abstract twenty cases in which electrocardiograms were taken during death, and in detail five other cases in which epinephrine (solution, 1:1,000) was injected into the heart after all deflections in the electrocardiogram had ceased.

In our series an attempt was made to obtain tracings in all three leads during the early events preceding death. After death, events were recorded only in lead II. In most of the cases, complete data were obtained including the time when the first tracing was taken, the time of clinical death as evidenced by cessation of respiration and audible heart sounds and also the time of occurrence of the last complex in the electrocardiogram. Factors such as age, sex and cause of death were also listed. Finally, the tracings were studied in detail and the



Fig. 1 (case 21)—Sequence of events showing the return of complexes after the injection of epinephrine into the heart.

outstanding features of each tabulated in order of occurrence. The data on the first twenty cases are summarized in the table. The last five cases, in which stimulation was employed, are not included in this group, but are described in detail. The entire group of twenty-five cases is considered in the comment.

#### REPORT OF SELECTED CASES

**CASE 21**—In a woman, aged 22, the cause of death was a gunshot wound of the neck (fig. 1).

*Analysis of Electrocardiograms*—Respiration and heart sounds ceased at 7:18 p. m. The record was begun at 7:19 p. m. The final complex occurred at 7:36 p. m. The first electrocardiograms were taken one minute after clinical death. They showed a sinus rhythm with a rate of 100 a minute. The complexes were essentially normal. As events proceeded, the rate gradually decreased and the P-R interval became prolonged. The S wave increased in depth and the high

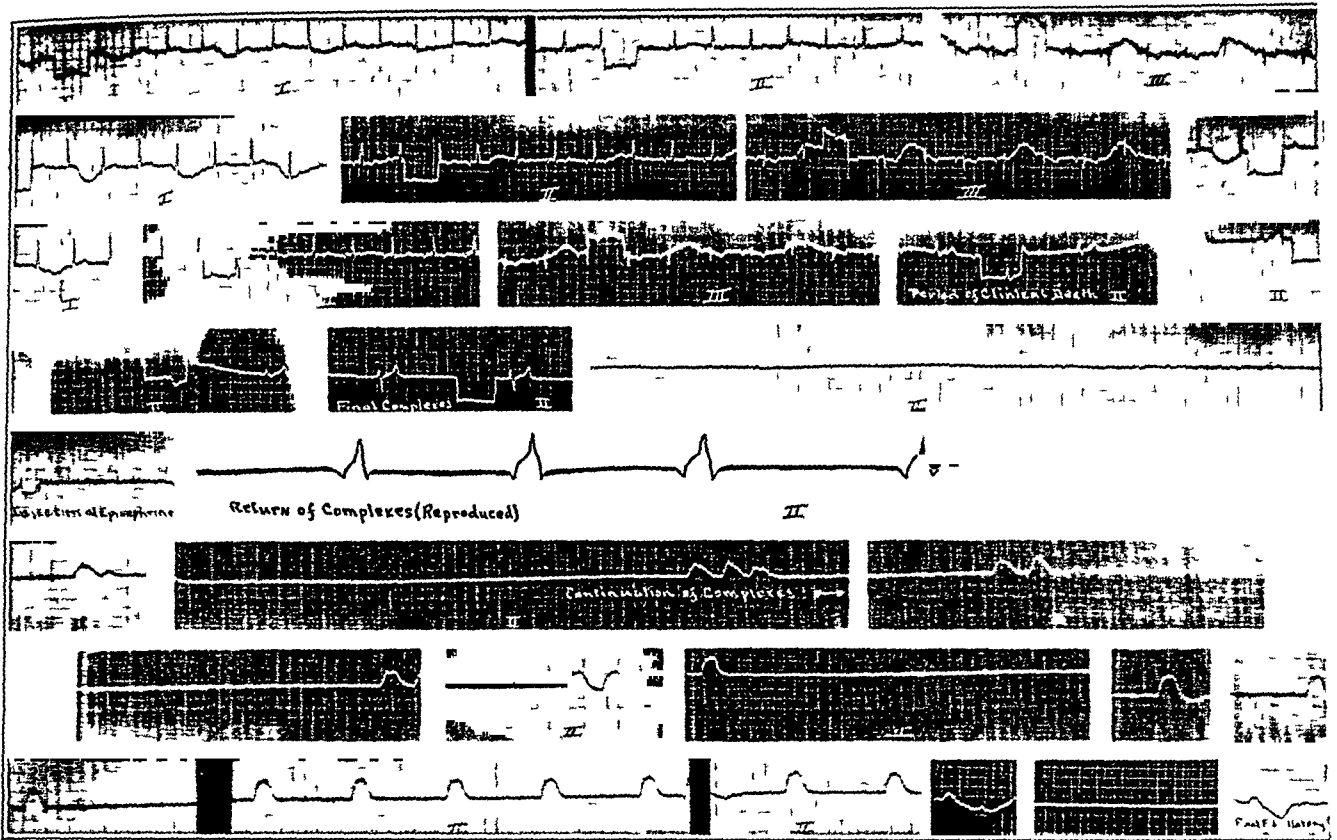


Fig 2 (case 22) —Sequence of events showing the return of complexes after the injection of epinephrine into the heart

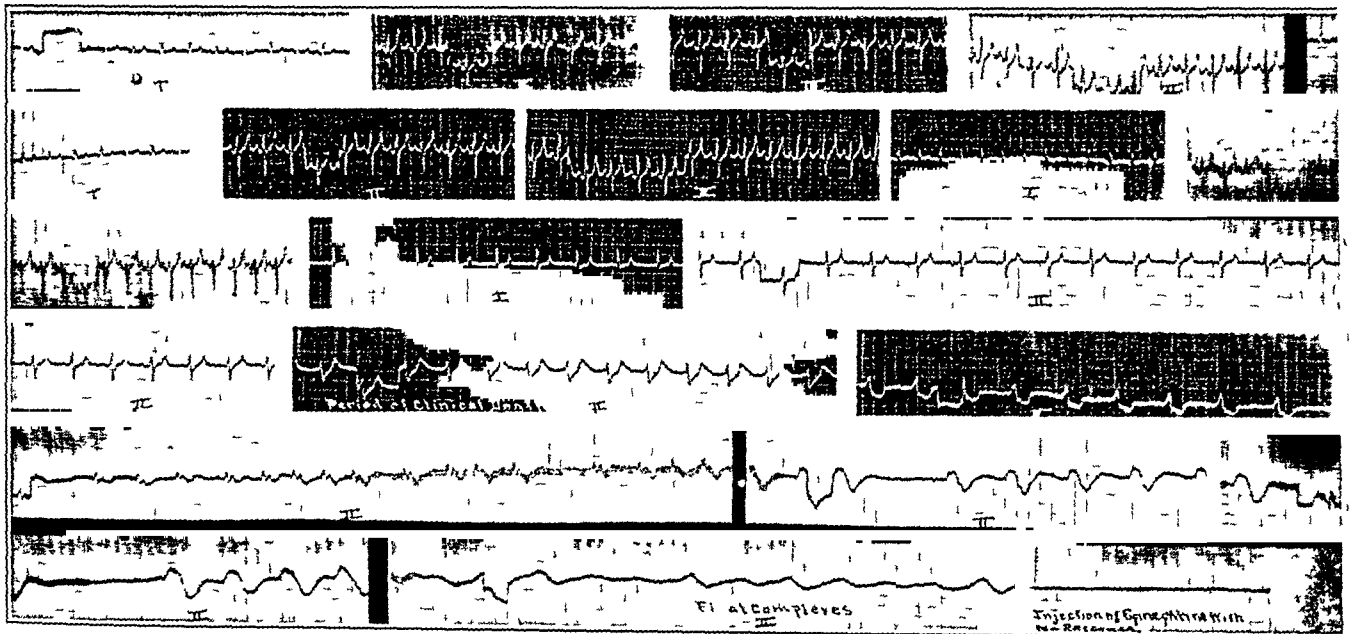


Fig 3 (case 23) —Sequence of events showing the failure of return of complexes after the injection of epinephrine into the heart



peaked T wave began below the iso-electric line. The final complexes were low monophasic deflections, apparently ventricular in origin. After a pause of approximately one minute, during which no further complexes occurred, epinephrine was injected into the heart. The site of injection was usually the third left interspace,

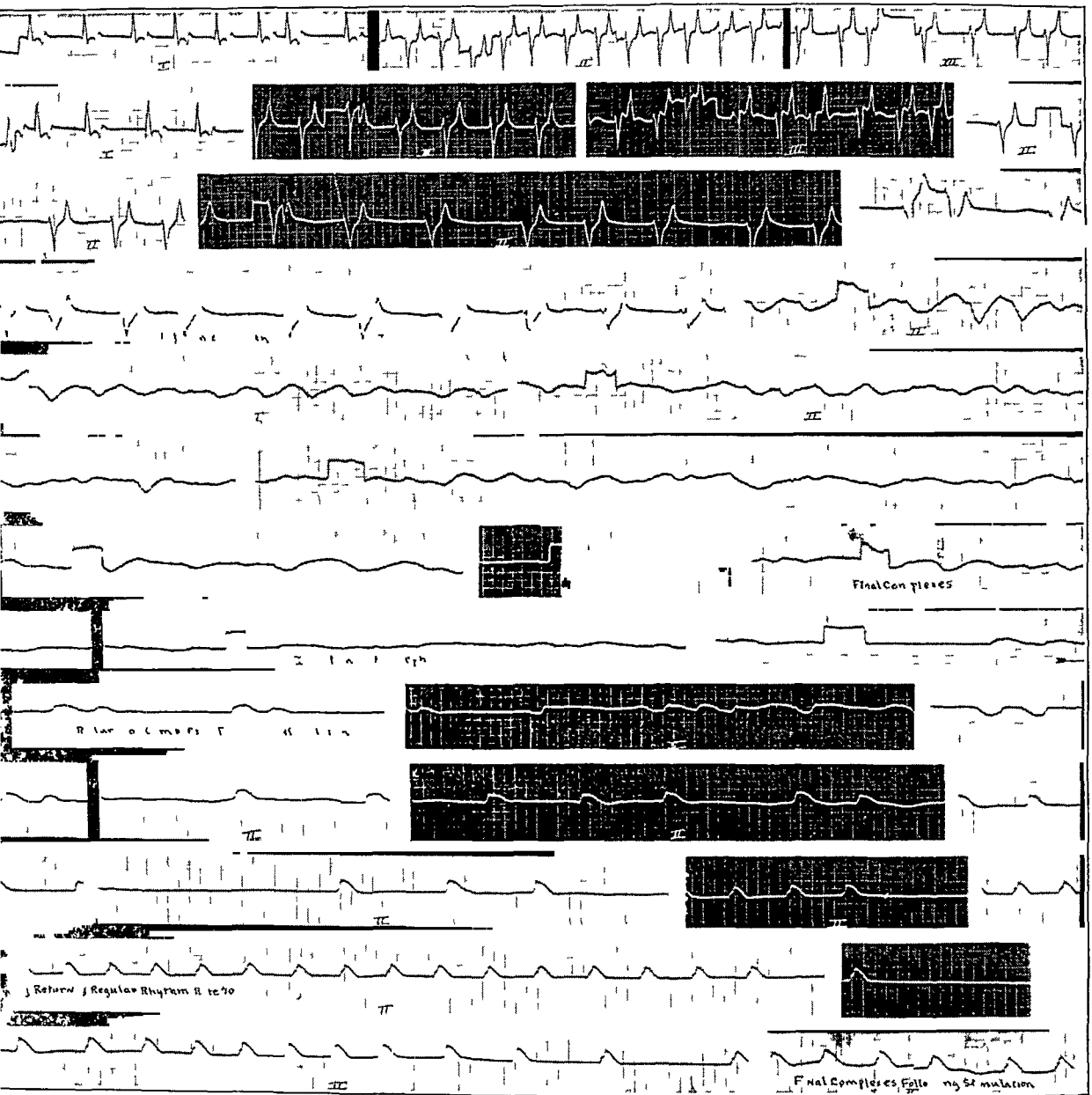


Fig 4 (case 24) —Sequence of events showing the return of complexes after the injection of epinephrine into the heart

close to the sternum. Injections were made here because of ease of administration and not with reference to any particular chamber of the heart. A needle measuring about 4 inches (10.1 cm) in length was used for this purpose, and was inserted until blood flowed back into an attached syringe. Doses of 2, 6 and 5 cc were injected at intervals of two minutes. Large doses were chosen arbitrarily. Seven minutes after the last injection three monophasic complexes of low amplitude

returned, similar in form to the original final complexes. They began eleven minutes after the original final complex and twenty-nine minutes after clinical death.

CASE 22—In a woman, aged 44, the cause of death was hypertensive cardiac disease and chronic nephritis (fig 2)

*Analysis of Electrocardiograms*—The record was begun at 8 30 a m. Respiration and heart sounds ceased at 9 55 a m. The final complex occurred at 9 56 a m. The first electrocardiograms were taken one hour and twenty-five minutes before death. They showed an inversion of the P waves in leads II and III, a biphasic T wave in lead II and an inverted T wave in lead III. The rate was 80 a minute. After clinical death the pacemaker became migratory, and varied between the sinus node and the junctional tissues. A slow nodal rhythm supervened and was followed by final complexes which were apparently nodal in origin. After a pause of approximately one minute, during which no further deflections occurred, 5 cc of epinephrine was injected into the heart. Five complexes, probably nodal in origin, returned. They developed very faintly on a faulty piece of film, and were reproduced as nearly as possible by hand. Injection of epinephrine

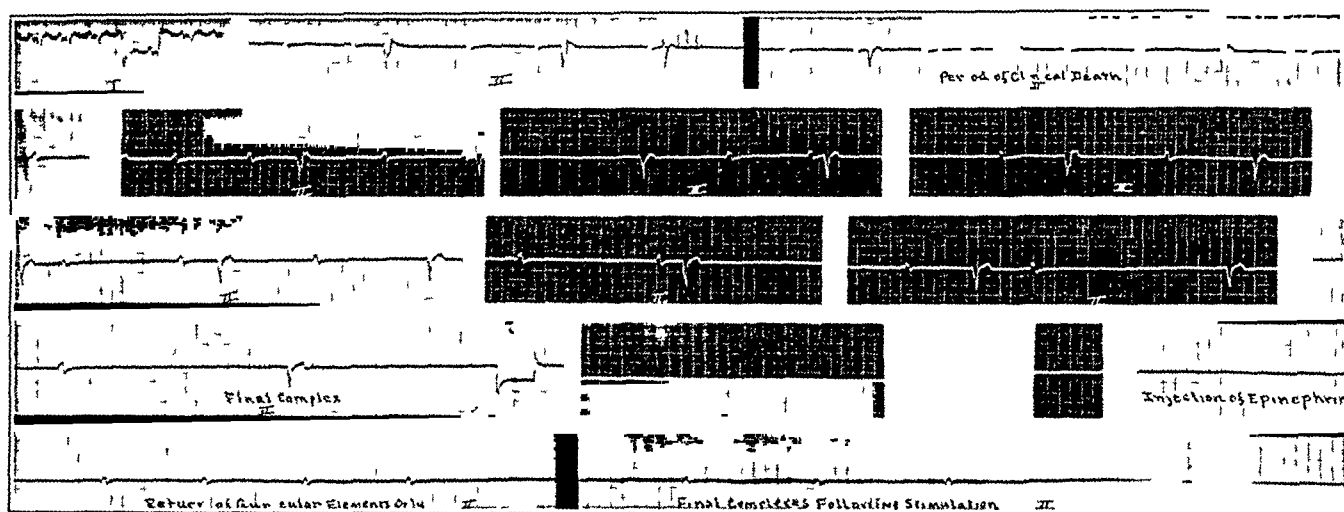


Fig 5 (case 25)—Sequence of events showing the return of complexes after the injection of epinephrine into the heart

in 5 cc quantities was repeated at short intervals and resulted finally in the return of irregularly spaced monophasic complexes. The last injection of epinephrine was given thirty-six minutes after the original final complex and thirty-seven minutes after clinical death. It initiated a series of low fibrillatory waves, apparently ventricular in origin.

CASE 23—In a man, aged 28, the cause of death was undetermined. The predominant finding was acute pulmonary edema (fig 3)

*Analysis of Electrocardiograms*—The record was begun at 10 48 a m. Respiration ceased at 1 32 p m and the heart sounds at 1 33 p m. The final complex occurred at 1 35 p m. The first electrocardiograms were taken two hours and forty-four minutes before death. They showed essentially normal complexes with a tall peaked T wave and a deep S wave in leads II and III. The rate was 110 a minute. There was left ventricular preponderance. The P wave became inverted for a short interval. After clinical death, the rate decreased progressively. No definite P waves occurred. The R waves were of low amplitude and the S waves were deep. The T waves were broad, began below the iso-

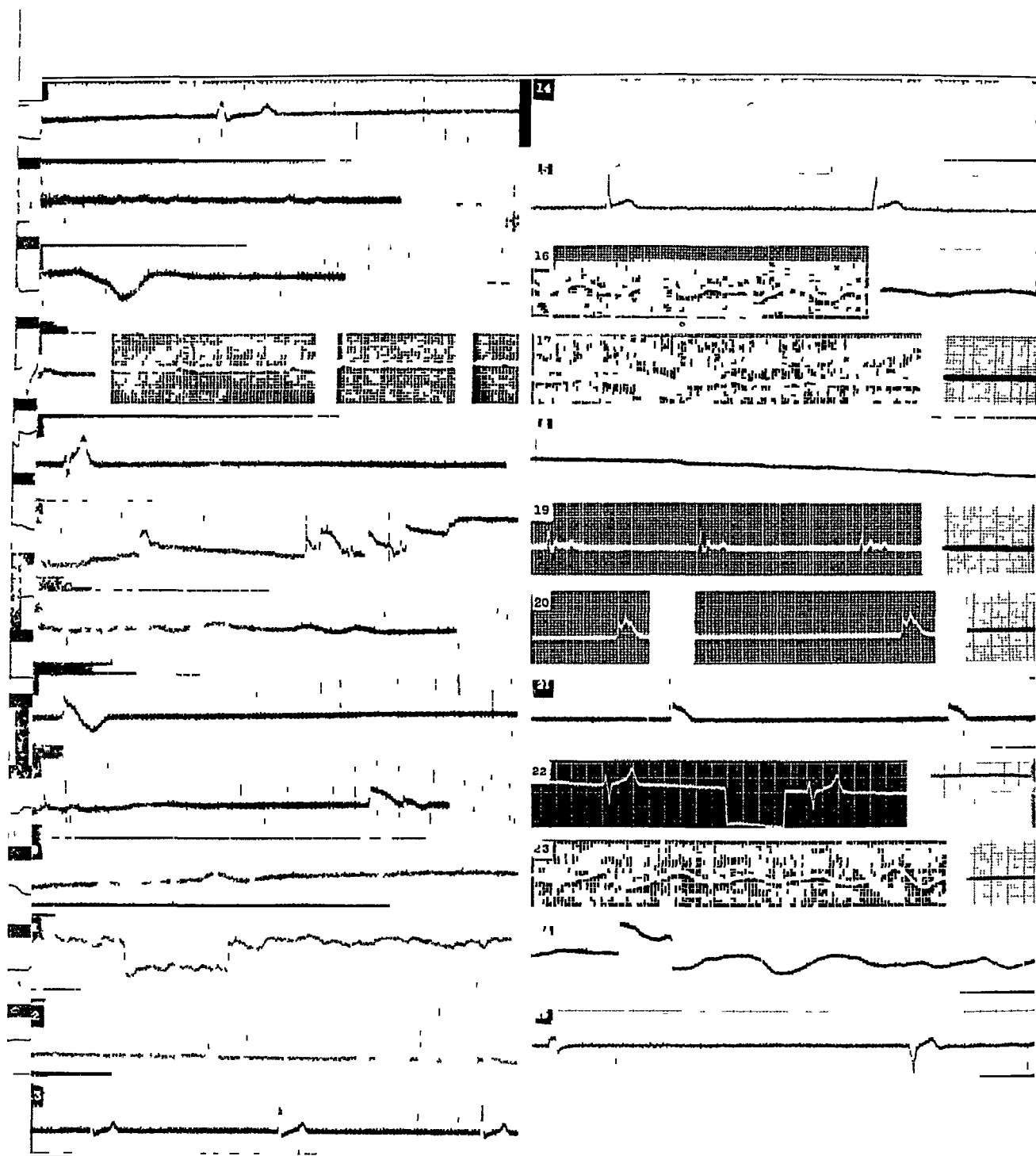


Fig 6 (cases 1 to 25) —Final complexes 1, nodal, 2, auricular, 3, ventricular, 4, ventricular, 5, ventricular, 6, ventricular, 7, ventricular, 8, ventricular, 9, ventricular, 10, ventricular, 11, ventricular, 12, auricular, 13, nodal, 14, auricular, 15, nodal, 16, ventricular, 17, undetermined, 18, auricular, 19, nodal, 20, ventricular, 21, ventricular, 22, nodal, 23, ventricular, 24, ventricular, and 25, nodal

electric line and finally rose above the R wave. The final complexes were large biphasic deflections, irregularly spaced and ended in low fibrillatory waves, apparently ventricular in origin. Two minutes after the final complex, epinephrine in 5 cc quantities was injected into the heart at short intervals. There was no response.

CASE 24—In a man, aged 40, the cause of death was chronic myocardial disease (fig 4).

*Analysis of Electrocardiograms*—The record was begun at 5 08 a m. Respiration ceased at 5 45 a m and the heart sounds at 5 47 a m. The final complex occurred at 5 49 a m. The first electrocardiograms were taken thirty-seven minutes before death. They showed a slow nodal rhythm. The rate was 50 a minute. No P waves were seen. The R waves were tall, the T waves began below the iso-electric line and were biphasic. An irregular nodal rhythm of 35 a minute occurred. The Q-R-S interval increased to 0.24 second. After clinical death the complexes changed to low fibrillatory waves, apparently ventricular in origin. After a pause of approximately one minute, 5 cc of epinephrine was injected into the heart. There was no response. Two minutes later the injection was repeated and resulted in the return of irregularly spaced monophasic complexes. They were followed by other monophasic complexes which, for a brief period, were regularly spaced and occurred at a rate of 75 a minute. These deflections probably arose in the ventricle. They finally became irregularly spaced and assumed the form of those occurring in ventricular fibrillation. They began twenty-seven minutes after the original final complex and thirty-one minutes after clinical death.

CASE 25—In a woman, aged 45, the cause of death was chronic myocardial disease (fig 5).

*Analysis of Electrocardiograms*—The record was begun at 3 22 p m. Respiration ceased at 3 27 p m and the heart sounds at 3 30 p m. The final complex occurred at 3 33 p m. The first electrocardiograms were taken five minutes before death. The rate was 90 and the complexes were essentially normal in lead I. Partial heart block occurred. The subsequent complexes were irregularly spaced and consisted of broad, high, notched P waves, followed by ventricular complexes of two types. One type consisted of a tall R wave, a deep S wave with notching on the upstroke and a T wave which originated above the iso-electric line and was poorly formed. The other type was of more normal appearance and consisted of a tall R wave, a deep S wave and an upright T wave which was rounded and began below the iso-electric line. The final complex was probably nodal in origin and was essentially normal in form. After a pause of approximately one minute, during which no deflections occurred, 2 cc of epinephrine was injected into the heart. The injections were repeated at intervals of one minute for two additional doses without response. Three minutes after the original injection, 2 cc of epinephrine resulted in a return of complexes. They consisted of auricular elements only and were low, broad and notched. The final auricular complex, following stimulation, began five minutes after the original final complex and twelve minutes after clinical death.

#### COMMENT

The findings in our cases differ in no marked degree from those reported by previous observers, except for the last five cases in which epinephrine was injected into the heart. We know of only one previous report of the electrocardiographic findings in attempts to resuscitate.

# Summary of Principal Events in Cases 1 to 20

Case	Sex	Age	Cause of Death	Time Elements				Origin Final Complex	Sequence of Events in Electrocardiogram
				Record Began	Respiration Ceased	Heart Sounds Ceased	Final Complex		
1	M		Chronic nephritis					A V node*	Auricular extrasystole, nodal rhythm with retrograde conduction, absent P waves, periods of auricular and ventricular asystole, final nodal standstill
2	M	14	Abscess of brain	7 40 p m			7 55 p m	Auricle	Sinus tachycardia, partial heart block, ventricular asystole, fibrillatory waves of auricle, final auricular standstill
3	M	30	Pulmonary tuberculosis	6 30 a m			6 45 a m	Ventricle	Nodal rhythm, decreased rate, idioventricular conduction defect, final ventricular standstill
4	M	25	Lobar pneumonia	10 25 a m	3 21 p m		3 24 p m	Ventricle	Sinus tachycardia, ventricular tachycardia, ventricular fibrillation, final ventricular standstill
5	F	55	Cerebral hemorrhage	1 10 a m	1 59 a m		2 03 a m	Ventricle	Sinus tachycardia, irregular nodal rhythm, migratory pace maker, ventricular extrasystole, final ventricular standstill
6	M	28	Pneumococcal meningitis	9 49 p m	9 50 p m		9 54 p m	Ventricle	Sinus tachycardia, ventricular extrasystole, partial heart block, ventricular asystole, complete heart block, auricular and ventricular asystole, ventricular fibrillation, final ventricular standstill
7	F	49	Lobar pneumonia	2/6/31 3 00 p m	2/7/31 2 40 p m			Ventricle	Normal tracing, ventricular extrasystole, nodal rhythm, ventricular tachycardia, ventricular fibrillation, final ventricular standstill
8	F	30	Septicemia		6 40 p m			Ventricle	Sinus tachycardia, nodal rhythm, idioventricular conduction defect, auricular and ventricular asystole, final ventricular standstill
9	F	18	Streptococcal meningitis	11 05 p m	11 05 p m	11 05 p m	11 40 p m	Ventricle	Normal tracing, lead I, ventricular fibrillation, recovery, ventricular fibrillation, recovery, auricular and ventricular asystole, ventricular fibrillation, auricular and ventricular asystole, ventricular fibrillation, final ventricular standstill
10	M	35	Unknown	9 00 a m	9 40 a m	9 40 a m	9 43 a m	Ventricle	Normal tracing, nodal rhythm, absence of P waves, return of P waves, nodal rhythm, ventricular tachycardia, ventricular fibrillation, final ventricular standstill
11	F	20	Miliary tuberculosis	5 00 p m	9 55 p m	9 55 p m	9 57 p m	Ventricle	Sinus tachycardia, nodal rhythm, ventricular tachycardia, ventricular fibrillation, final ventricular standstill

*Summary of Principal Events of Cases 1 to 20—Continued*

Case	Sex	Age	Cause of Death	Time Elements				Origin Final Complex	Sequence of Events in Electrocardiogram
				Record Began	Respiration Ceased	Heart Sounds Ceased	Final Complex		
12	M		Fractured skull	11 09 p m	11 20 p m	11 20 p m	11 24 p m	Auricle	Normal tracing, ventricular escape, ventricular asystole, ventricular tachycardia, final auricular standstill
13	F		Intestinal obstruction	7 15 a m	8 10 a m	8 10 a m	8 13 a m	A V node*	Sinus tachycardia, normal rhythm, nodal rhythm, final nodal standstill
14	F	32	Septicemia	9 00 a m	12 00 noon	11 58 a m	12 06 p m	Auricle	Sinus tachycardia, idioventricular conduction defect, terminal fibrillatory waves, probably auricular in origin, final auricular standstill
15	M	43	Rupture of aneurysm	9 32 a m	9 36 a m	9 38 a m	9 43 a m	A V node*	Nodal rhythm, sinus rhythm, auricular and ventricular asystole, nodal rhythm, sinus rhythm, partial heart block, nodal rhythm, final nodal standstill
16	M	40	Lobar pneumonia	11 37 a m	11 38 a m	11 39 a m	11 41 a m	Ventricle	Nodal rhythm, ventricular fibrillation, auricular and ventricular asystole, ventricular fibrillation, final ventricular standstill
17	F	30	Chronic myocardiac disease	3/5/31 5 00 p m	3/6/31 12 25 a m	12 25 a m	12 28 a m	Undetermined	Sinus tachycardia, partial heart block, sino auricular block, nodal extrasystole, nodal rhythm, final complexes with auricular and ventricular elements
18	M	22	Lobar pneumonia	11 06 a m	11 27 a m	11 28 a m	11 31 a m	Auricle	Sinus tachycardia, nodal rhythm, migratory pacemaker, nodal extrasystole, partial heart block, ventricular asystole, final auricular standstill
19	F	47	Hypernephroma	6 20 a m	6 33 a m	6 33 a m	6 36 a m	A V node*	Sinus tachycardia, changing form of P wave, sino auricular block, nodal rhythm with retrograde conduction, final nodal standstill
20	M	30	Lobar pneumonia	4 00 p m	6 32 p m	6 36 p m	6 42 p m	Ventricle	Sinus tachycardia, nodal rhythm, idioventricular conduction defect, final ventricular standstill

\* Auriculoventricular node

tate the dying human heart with intracardiac injections of epinephrine Levine and Matton<sup>4</sup> reported a case of the Adams-Stokes syndrome in which ventricular fibrillation occurred for a period of three and a half minutes and was followed by ventricular standstill for seventy-nine seconds. The rhythm returned to normal after the intracardiac injection of 0.5 cc of epinephrine hydrochloride (solution, 1:1,000).

<sup>4</sup> Levine, S. A., and Matton, Marcel. Observations on a Case of Adams-Stokes Syndrome, Showing Ventricular Fibrillation and Asystole Lasting Five Minutes With Recovery Following the Intracardiac Injection of Adrenalin, *Heart* 12:271, 1926.

The patient was able finally to leave the hospital, but died a short time later, presumably from a similar attack. This case differs from those which we report in that P waves continued to occur in the electrocardiograms after death, whereas in our cases there was standstill of both auricles and ventricles before stimulation was employed. Levine's and Matton's patient lived, whereas we were unable to restore our patients to life after complete cardiac standstill.

In our series, there were thirteen male and twelve female patients (table). The causes of death varied. The age limits ranged from 14 to 55 years. The period elapsing from clinical death to the final complex averaged five minutes. The longest individual period was thirty-five minutes.

A consideration of the arrhythmias occurring during the sequence of events is interesting. Heart block in some form occurred in seven cases. Sino-auricular block occurred twice. Premature contractions occurred in ten cases, being of auricular origin in one case, nodal in four cases and ventricular in five cases. Auricular fibrillation did not occur definitely. Ventricular fibrillation occurred in ten cases. In two cases there were temporary periods of recovery from fibrillation, and in one case there were four distinct periods of fibrillation. It was the terminal event in cessation of cardiac activity in nine of the twenty-five cases. Nodal rhythm was quite common and occurred in sixteen cases. Periods of asystole of either auricle or ventricle or both occurred in ten cases. The average asystolic period was from ten to fifteen seconds while the longest period was thirty-five seconds. Complexes resembling ventricular tachycardia occurred in four cases. Intraventricular conduction defects occurred in five cases.

The site of origin of final complexes varied (fig 6). It is difficult in the short tracings shown to judge the site of origin of the final complexes. Interpretation was based, in some instances, on preceding tracings, and therefore may not be obvious from the tracings reproduced here. As near as could be determined, the final complex, before stimulation, arose in the ventricle in fourteen cases, at the auriculoventricular node in six cases and in the auricle in four cases, and it was undetermined in one case. The final complex after stimulation in the last five cases differed from the original final complex in two cases. In case 22, ventricular fibrillation, which had not been present before stimulation, occurred as a terminal event after stimulation. In case 25, the final complex after stimulation was auricular in origin, whereas before stimulation it had been nodal in origin.

The usual sequence of events was that the tracings began with sinus tachycardia, which was followed by progressive slowing of the rate. Usually a slow nodal rhythm followed clinical death. A large number

of tracings manifested variations in the irritability of the sinus node. The pacemaker was frequently migratory in type, and shifted between the sinus node and the auriculoventricular node. Short periods of asystole occurred frequently. Heart block and extrasystoles were the common arrhythmias. Ventricular fibrillation was a frequent terminal event, preceding standstill of the heart.

The last five cases of our series are worthy of special consideration. In four cases we were able to cause a return of complexes with epinephrine after standstill of both auricles and ventricles. The electrocardiograms of case 24 (fig 4) are of particular interest. They show a momentary return of a regular rhythm with monophasic complexes, probably of ventricular origin. Each complex seems to be formed by a fusion of the R and T waves. These complexes finally become irregularly spaced and are converted into waves, interpreted as those of ventricular fibrillation.

Hyman,<sup>5</sup> in a recent review of the literature on resuscitation of the stopped heart by intracardiac therapy, concluded that stimulation may be applied most effectively to the right auricle because the impulse for contraction originates there. He thought that stimulation of the ventricle might lead to ventricular fibrillation, which is incompatible with life. The reverse would not be true necessarily, should the auricles fibrillate. Injections into the heart muscle were considered to be more effective than those made into the cavities of the heart or the pericardium. The response of the heart was not considered to be specific for any pharmacodynamic action, as a wide variety of drugs had been used for injection. The success of intracardiac therapy seemed to depend more on the irritant effect of puncturing the heart muscle with the injecting needle than on the substance injected. Hyman considered that the work of Meyer<sup>6</sup> and others suggested that all hearts in which cardiac arrest had occurred could be divided into two groups. In group 1 was placed the healthy asystolic heart that stops under narcosis, anesthesia, shock, accident, injury and collapse, while in group 2 may be placed the pathologic heart suffering from the effects of acute and chronic disease with resulting myocardiac degeneration and general vasomotor breakdown. A review of successful cases indicated that intracardiac therapy should be most effective in group 1, while failure would most likely occur in group 2.

Interpretation of our results is a difficult task. The investigations of Hyman suggest that in our case 21, injections were possibly made

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5 Hyman, A. S. Resuscitation of the Stopped Heart by Intracardiac Therapy, *Arch Int Med* **46** 553 (Oct) 1930.

6 Meyer, C. *Jahrb f Kinderh* **107** 76, 1924.



into the ventricle and resulted in the return of ventricular deflections. Possibly this happened also in cases 22 and 24, and resulted in the onset of ventricular fibrillation. In case 25, the injecting needle may have reached the auricle, as the returning deflections were auricular in type. Since four of our five patients belonged to group 2, in which resuscitation of the heart is not to be expected, our lack of success may be partially explained. Other factors should be considered, however. The large doses of epinephrine used may have had a damaging effect on the myocardium. The effect of anoxemia on the heart muscle and the vital brain centers, controlling respiration and vasomotor activity, should be considered. When the heart muscle and these vital centers have not been deprived of oxygen too long, resuscitation may occur, but if the period of asphyxia has been prolonged, resuscitation is improbable because of the fatal effects of the anoxemia.

The significance of complexes occurring in electrocardiograms taken after clinical death is unexplained. Whether these complexes are an indication of contraction of the heart muscle or whether they represent the spread of an excitation wave without muscular contraction is undetermined. If these complexes which may occur for long periods are an indication of contraction of the heart muscle after death, it is possible that they exert sufficient pressure on the aortic leaflets to permit a sufficient flow of blood in the cerebral and coronary arteries to maintain life for a brief period of time. This would tend to explain the clinical reports of patients being revived as long as thirty minutes after apparent death. In our cases, in which stimulation was delayed until all cardiac contractions had ceased and no further complexes occurred, the nutrition of the brain and heart muscle was probably impaired to such an extent that resuscitation was not possible, even though a few feeble contractions followed the injection of epinephrine into the heart.

The demonstration of the response of the heart muscle to intracardiac therapy, after prolonged asphyxia, increases interest in the problem of cardiac resuscitation. Further investigations are needed to determine the significance of contractions of the heart muscle after death, with the possibility of cerebral and coronary flow. It is obvious that investigations of this type are best adapted to animal experimentation.

#### SUMMARY

- 1 Twenty-five cases are reported in which electrocardiograms were taken during death. This series makes a total of ninety-five reported cases.

- 2 Our series is analyzed briefly with regard to age, arrhythmias, sequence of events and final complexes.

3 The last five cases are described in detail and show the effect of injecting epinephrine into the heart after all contractions had ceased and the heart was at a complete standstill. In four cases, electrocardiograms showed that complexes returned following stimulation.

4 The demonstration of the response of the heart muscle to stimulation after prolonged asphyxia increases interest in the problem of cardiac resuscitation.

# DIFFUSE AMYLOIDOSIS

THREE UNUSUAL CASES A CLINICAL AND PATHOLOGIC STUDY

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The occurrence of diffuse amyloidosis among patients suffering from chronic sepsis, tuberculosis, syphilis and certain malignant diseases has long been recognized, and it should be suspected in the presence of these conditions if hepatic or splenic enlargement or evidences of renal involvement are noted

In the absence of disease ordinarily bearing an etiologic relationship to amyloidosis, however, this condition probably often escapes recognition because it is not suspected. Atypical cases of amyloidosis which may be of obscure origin do occur. Three unusual cases of diffuse amyloidosis are herewith presented. Case 1 has been reported previously,<sup>1</sup> and we are including only an abstract of it

## REPORT OF CASES

**CASE 1—History**—A Mexican, aged 38, was admitted to the Mayo Clinic on Jan 28, 1929, at which time a diagnosis of lymphosarcoma of Hodgkin's type was made. This was confirmed by histologic studies of one of the enlarged cervical nodes. Roentgen treatment was given, and because of the vague abdominal symptoms and because the patient's apparent illness was somewhat out of proportion to the amount of objective evidence of Hodgkin's disease, the entire neck, thorax, abdomen and back were irradiated. The response to treatment by roentgen rays was striking.

**Examination**—The patient returned for examination on May 29. His condition was still much improved, but because he was complaining of thoracic pain, and because of the slight residual cervical adenopathy on the left and a questionable small, tender mass deep in the epigastrium, he was again given intensive treatment by roentgen rays, and again his condition improved promptly. He was readmitted to the clinic on December 12, but this time he presented an entirely different appearance. No evidence of the previous Hodgkin's disease was demonstrable, but he had lost weight and was weak and toxemic, although not appreciably anemic or cachectic. On both previous admissions his cardiorenal-vascular

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From the Division of Medicine and the Section on Pathologic Anatomy, the Mayo Clinic

1 Bannick, E G, and Nelson, W B. Diffuse Amyloidosis of Unknown Etiology, M Clin North America **14** 773 (Nov) 1930

status had apparently been entirely normal, but this time urinalysis disclosed severe albuminuria, mild hematuria and a few hyaline and waxy casts. The specific gravity of the urine, in spite of the severe albuminuria, was only 1.015. The blood pressure in millimeters of mercury was 100 systolic and 70 diastolic. Excretion of phenolsulphonphthalein was 15 per cent in one hour. The value for blood urea was 58 mg for each hundred cubic centimeters. The concentration of hemoglobin was 75 per cent, erythrocytes numbered 4,360,000 and leukocytes 8,100 in each cubic millimeter of blood. The differential leukocyte count was essentially normal. There were 3.8 Gm of serum protein for each hundred cubic centimeters, of which 27 per cent was albumin. The value for blood cholesterol was 235 mg for each hundred cubic centimeters.

Because of the unusual renal picture the possibility of amyloid disease was considered and will be commented on later. A congo red test was strikingly positive. More than 75 per cent of the congo red that was injected intravenously (18 cc of a 1.5 per cent solution) had disappeared from the blood stream at the end of an hour, practically no dye was demonstrable in the urine at the end of an hour and very little in five hours. This made the diagnosis of amyloidosis likely, and although the liver was not perceptibly enlarged, there was marked retention of bromsulphalein, indicating extensive involvement of this organ.

*Course of Illness*—In spite of attempts at treatment, the patient failed rapidly and died on the twelfth day after admission. At the end he resembled a patient in a crisis of Addison's disease, with vomiting, extreme restlessness, falling blood pressure, and weak cardiac sounds. The value for blood urea on the day before death was 56 mg for each hundred cubic centimeters. A diagnosis was made of diffuse amyloidosis with renal and hepatic insufficiency and a possibility of suprarenal insufficiency.

*Necropsy*—The complete records of necropsy, including photomicrographs of a section of the kidney, were given in the original report. The final anatomic diagnosis was (1) lymphosarcoma (Hodgkin's type) of the prevertebral and pancreatic lymph nodes and liver (small nodule), (2) amyloidosis of the spleen, kidneys, liver, suprarenal glands, ileum and colon, (3) healed duodenal ulcer, and (4) pseudomembranous enterocolitis.

*CASE 2—History*—A man, aged 44, was admitted to the clinic on Dec 13, 1931. In the two years previous to his admission he had been troubled with indigestion, the symptoms of which were sour stomach, a sense of fulness, some pain and distress after meals and considerable bloating. These symptoms followed ingestion of any type of food. At certain times, however, he was able to eat without distress. Six months before his admission the symptoms of indigestion had become considerably exaggerated, and on examination the liver had been found to be enlarged. At that time he entered a hospital for examination, and in the course of his stay he had begun to vomit following meals and to fail in strength. A diagnosis of cirrhosis of the liver had been made, although the question of Hodgkin's disease had been raised because of some enlargement of the inguinal and axillary nodes and because he had been annoyed by considerable pruritus without jaundice.

In October, 1931, two and a half months before the patient's admission to the clinic, surgical exploration had been carried out. The report stated that the liver was smooth, did not look cirrhotic grossly, and yet was definitely enlarged and abnormal. Biopsy of a specimen from the liver had disclosed some changes that were difficult to interpret, but which suggested chronic hepatitis. The gallbladder, although appearing normal, was drained. Convalescence from the surgical procedure had been slow. During the first few days of ambulatory convalescence, the abdomen had gradually become enlarged. Shortly after this, the patient had

experienced abdominal pains, more severe than at any time previously, and at that time the possibility of appendicitis was considered, but the attack was atypical and operation was deferred. Following this attack, the genitalia had been edematous, and then edema of the lower extremities had occurred for the first time. Finally, general anasarca had developed. Before he came to the clinic the patient had received two intravenous injections of merbaphen, one of which had produced slight diuresis, and the other, diarrhea.

*Examination*—At the time of the patient's admission to the clinic, he was complaining chiefly of bloating and a sensation of abdominal pressure. He was weak, and he walked with much difficulty. He appeared to be very ill and somewhat anemic. The abdomen was tense with ascites. The liver was large and very firm. The blood pressure was 90 systolic and 55 diastolic. Neurologic examination disclosed generalized decrease in activity of all deep reflexes and positive bilateral Babinski and Hoffmann signs. There was dysarthria, with slurring speech. It was felt that from a neurologic standpoint there was no definite evidence to indicate syphilis or to aid in the diagnosis. Albuminuria was graded 2 to 3. Erythrocytes in the urine were graded 1 to 2, and there was an occasional pus cell and some hyaline casts. Excretion of phenolsulphonphthalein varied from 15 to 25 per cent in one hour and fifteen minutes. Erythrocytes numbered about 4,000,000 and leukocytes 10,200 in each cubic millimeter of blood. The value for urea was 56 mg in each hundred cubic centimeters of blood, the carbon dioxide-combining power of the plasma and the value for plasma chlorides were normal. On a test of hepatic function, retention of bromsulphalein was graded 1, but the response to the galactose tolerance test was normal. The value for bilirubin was 1.5 mg in each hundred cubic centimeters of serum, and the van den Bergh reaction was indirect. The basal metabolic rate was  $-18$ . The ocular fundi were normal. During the twenty-eight days that the patient was under observation his pulse rate was normal and his temperature definitely subnormal.

*Operation and Course*—On the eighteenth day after the patient's admission, abdominal paracentesis was done, 2,000 cc of straw-colored fluid being removed. Microscopic study of this fluid disclosed that most of the cells were leukocytes. The course of the illness was progressively downward almost from the date of admission to the clinic. About a week after admission slight jaundice developed. This became progressively more pronounced, so that the value for bilirubin rose to 9.4 mg for each hundred cubic centimeters of serum, and the van den Bergh reaction became direct.

There was a steady rise in the value for blood urea until it reached 549 mg shortly before death. Analysis of the urine daily disclosed persistently marked albuminuria, for the most part graded 3, and presence of erythrocytes was graded 1 to 2. Throughout this period marked hypotension was a feature of note. Most of the time the blood pressure was about 65 systolic and 40 diastolic, and readings as low as 55 systolic and 40 diastolic were obtained. This suggested suprarenal insufficiency, and the manner of the patient's decline simulated that which occurs in the terminal crisis of Addison's disease. Finally, there developed hiccup, diarrhea, delirium and coma, and the patient died twenty-eight days after admission. During the last days of his life, he manifested a combination of profound renal, suprarenal and hepatic insufficiency, the cause of which remained undetermined. Necropsy was performed three hours after death.

*Necropsy*—Icterus, graded 2, was present. The peritoneal cavity contained 3,000 cc of clear yellow fluid. The pleural cavities contained clear yellow fluid, there being 800 cc in the right and 300 cc in the left. The heart weighed 379 Gm. The

consistence of the muscle was increased. It was friable and waxlike. The lungs were edematous and congested. The spleen weighed 500 Gm. It was slate gray, with reddish mottling. The consistence was increased. The normal splenic markings were obscured and the surface was wavy. The application of iodine revealed a rapidly developing change from dark brown to almost black. The typical reddish-brown hue, which usually characterizes amyloid deposits, did not appear. The liver weighed 3,187 Gm. The capsule was smooth. The color was brownish red, and the consistence was increased. The sectioned surface was wavy in appearance. The lobular markings were poorly shown. The accessory portal veins were of increased prominence. The veins in the lower portion of the esophagus were also dilated. The lymph nodes about the head and body of the pancreas were slightly enlarged and firm. The left kidney weighed 174 Gm, and the right, 180 Gm. The cortical surfaces appeared somewhat granular. Their consistence was slightly increased. Iodine tests were applied to the cardiac muscle, liver, suprarenal glands and kidneys, with a response similar to that described for the spleen. The muscle cells of the myocardium, when examined microscopically,<sup>2</sup> revealed marked atrophy. The stroma was increased because of narrow bands of hyaline deposits. In some areas wide zones were seen where muscle cells had entirely disappeared. In the sections stained with congo red this hyaline intercellular substance had a marked affinity for the dye. The walls of some pulmonary alveoli and of many blood vessels contained acellular deposits of hyaline material which stained bright red with congo red. The normal structure of the spleen was transformed by diffuse deposition of hyaline substance. The distinctive malpighian corpuscles were entirely gone, as well as practically all other pulp and stroma cells. The sinusoidal spaces were greatly decreased in number, and between surviving spaces, hyaline, eosin-staining deposits appeared (fig 1 A). With congo red the sections were stained diffusely red, with the exception of the nuclei and cytoplasm of cells. Methyl violet gave the characteristic amyloid reaction, but not so consistently as sections stained with congo red. Iodine alone or iodine and sulphuric acid failed to elicit a typical amyloid reaction in several trials. Sections taken from all lobes of the liver revealed extensive atrophy of the hepatic cords, between which was an accumulation of hyaline substance beneath the sinusoidal membrane (fig 1 B). Bile thrombi were present in the centers of the lobules. The hyaline substance was most clearly demonstrated by staining with congo red. With methyl violet, the reaction was suggestive of amyloid, but not so well revealed. Iodine alone or iodine and sulphuric acid failed to produce typical reactions. In the walls of the blood vessels and connective tissue of the stomach and duodenum, deposits of hyaline material gave a positive reaction with congo red. In the pancreas there was considerable hyaline transformation in the walls of blood vessels, in the interstitial connective tissue and, to some extent, focally about the pancreatic acini and in the islands of Langerhans. Staining with congo red made the change more evident. Sections of the kidneys revealed that all of the glomeruli were involved to some degree by isolated hyaline masses seen beneath the capillary basement membranes (fig 2 A). Similar changes also were found in the walls of arteries throughout both the cortex and the medulla and also in the intertubular stroma. Subcapsular zones of the cortex revealed, in

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2 The tissues in case 2 and 3 were fixed in Orth's fluid, from which paraffin sections were prepared. These sections were stained with both hematoxylin-eosin and with congo red. Routine descriptions were of sections stained with hematoxylin-eosin, supplemented by descriptions of sections stained with congo red. Frozen sections of tissues fixed in formaldehyde were also made and stained with methyl violet and iodine.

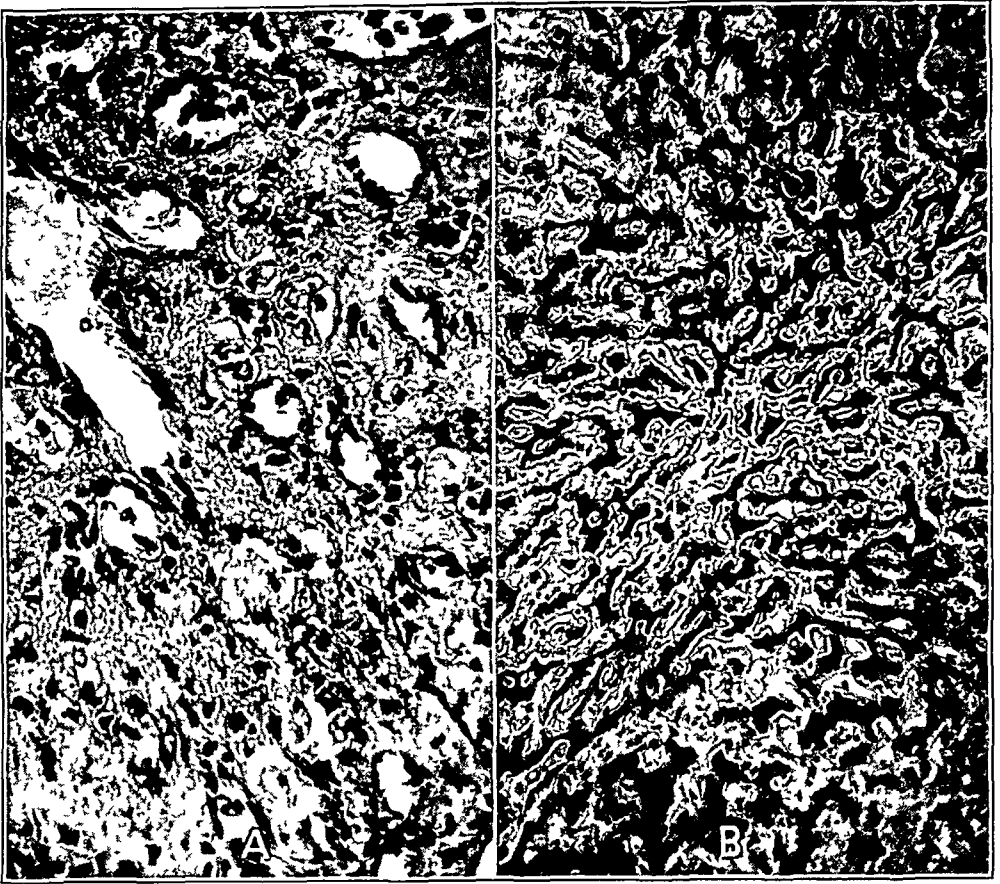


Fig 1 (case 2) —*A*, diffuse hyaline deposits in the spleen, *B*, diffuse hyaline deposits in the liver, with atrophy of hepatic cells

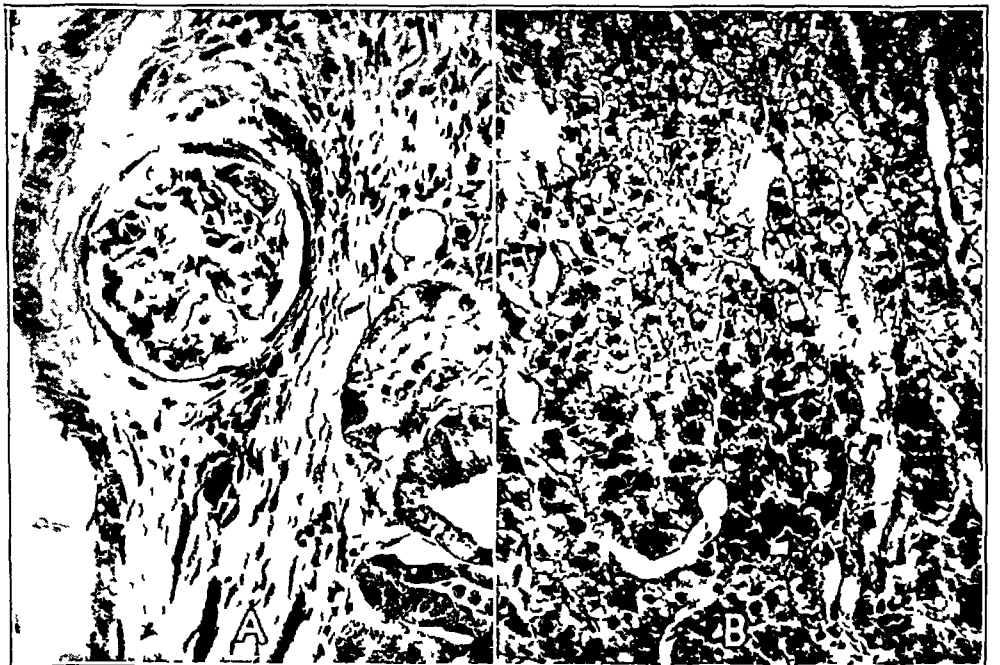


Fig 2 (case 2) —*A*, deposits of hyaline substance in a glomerulus Granular degeneration of tubular epithelium, *B*, hyaline deposits in a suprarenal gland Atrophy of cortical cells

addition, focal parenchymal atrophy with collections of lymphocytes. Epithelial cells, particularly of the convoluted tubules and Henle's loops, were swollen and contained multiple, small, eosinophilic granules. With congo red stain the hyaline substance was clearly revealed in the glomeruli, in intertubular zones and in the connective tissue of the cortical scars, as a homogeneous hyaline substance which stained bright red. Methyl violet revealed the hyaline material as light red. It was less apparent by this stain than by congo red. Large amounts of hyaline material, in bands, appeared in the suprarenal cortex, between the rows of cortical cells. Considerable atrophy of cortical parenchyma was present (fig 2B). The medulla presented accumulations of hyaline deposits surrounding the vascular channels. The deposits stained characteristically with congo red. The structure of the mesenteric and pancreatic lymph nodes was replaced by an almost uniform deposit of hyaline substance beneath the sinusoidal basement membrane, accompanying general atrophy of the lymphoid cells. Staining with congo red revealed this change best. The interacinar tissue of the thyroid gland was increased in prominence, with corresponding atrophy of glandular substance, owing to homogeneous eosin-staining deposits, which gave a positive amyloid reaction with congo red.

The anatomic diagnosis was as follows: (1) generalized amyloidosis, involving the spleen, liver, suprarenal glands, myocardium, lymph nodes, kidneys, pancreas, thyroid gland, lungs, thymus, stomach and other organs, (2) hypertrophy of the liver (3,187 Gm, normal, 1,800 Gm) with atrophy of hepatic cells, icterus and ascites (amyloid), (3) hypertrophy of the spleen (500 Gm, normal, 150 Gm, amyloid), (4) bilateral hydrothorax and edema of the lungs, (5) focal atrophy of the kidneys (amyloid, chronic pyelonephritis), (6) acute tubular degeneration of the kidneys, (7) cholelithiasis (one stone), (8) healed tuberculosis of the hilar nodes of the lungs, and (9) arteriosclerosis, graded 2.

**CASE 3—History**—A man, aged 55, was admitted to the clinic on April 5, 1932. He stated that he had felt very well until some time in the late summer of 1931, when he had begun to have epigastric discomfort which consisted of accumulation of gas, distress and a sensation of fulness occurring immediately after meals. Shortly after the onset of illness he had begun to notice shortness of breath on exertion, occasional dizzy spells and the need of urinating two or three times nightly, without other urinary symptoms. In January, 1931, he had noticed edema of the lower extremities, and at about the same time troublesome diarrhea had developed and persisted. He had consulted a physician as to treatment for the diarrhea and the edema, but a diagnosis had not been made. At this time he had begun to experience real epigastric pain for the first time, which occurred from two to three hours after meals, and occasionally awakened him at night. In February, edema of the left hand, arm and genitalia had developed. In March, the gastric discomfort after meals again had become more troublesome, and at that time he had begun to notice marked anorexia, nausea and, on a few occasions, vomiting. He had become progressively weaker and had lost flesh, and the edema had gradually increased.

**Examination**—On examination the patient appeared to be anemic and somewhat cachectic. There was marked edema of the lower extremities, genitalia and left arm and hand. A moderate amount of ascites, with considerable edema of the abdominal wall and back, was observed. The blood pressure was 90 systolic and 60 diastolic, in millimeters of mercury. Daily urinalysis revealed albuminuria, graded 2 to 3. The test for bile was always positive. Hyaline casts were present, graded 2 to 3 in all specimens. There were occasional erythrocytes in a few specimens. The specific gravity was normal, ranging from 1.012 to 1.026 and averaging



around 1 020 Excretion of phenolsulphonphthalein was 50 per cent in one hour and fifteen minutes The concentration of hemoglobin was 68 per cent (Dare) , erythrocytes numbered 3,700,000 and leukocytes, 4,800 in each cubic millimeter of blood The value for urea on two occasions was 18 and 20 mg in each hundred cubic centimeters of blood The concentration of cholesterol was 130 mg in each hundred cubic centimeters of blood, and the value for proteins, 3 Gm in each hundred cubic centimeters of serum The value for bilirubin was 17 mg in each hundred cubic centimeters of serum, and the van den Bergh reaction was direct The stool was normal The ocular fundi were normal, except for slight attenuation of the retinal arteries Because of the patient's weakened condition, roentgenograms of

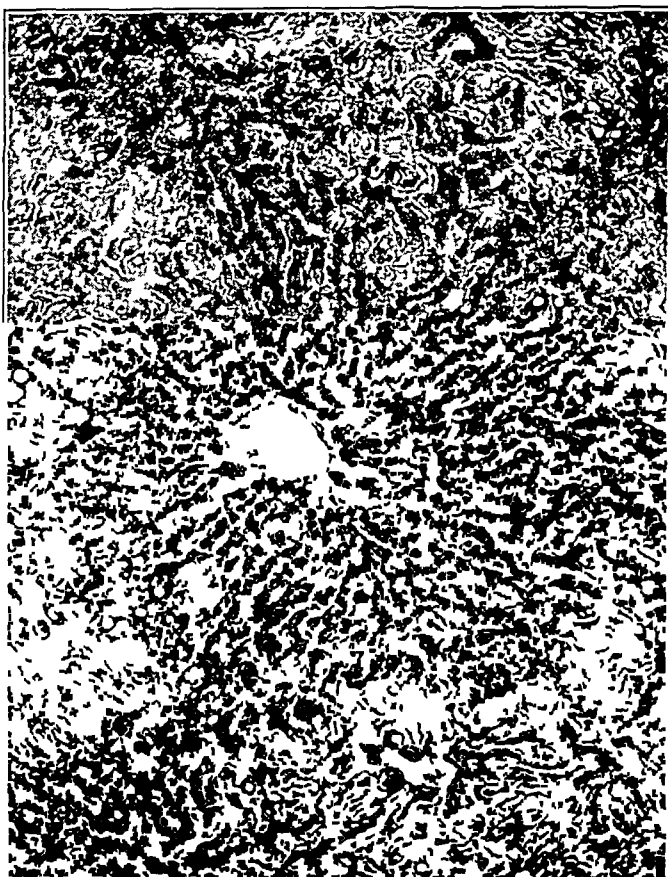


Fig 3 (case 3) —Deposits of amyloid about the periphery of the hepatic lobule

the stomach were not made, even though the history indicated disease of the stomach The basal metabolic rate was  $-8$  per cent

*Course*—During the two weeks that this patient was in the hospital under our observation, the temperature and pulse rate remained normal The condition did not improve, however, and soon he began to fail He refused to take adequate nourishment and did not respond to any form of symptomatic or diuretic treatment All laboratory data pointed to chronic nephrosis, but this did not satisfactorily explain his appearance and certain other features He looked too sick and cachectic for this diagnosis, and a malignant condition was suspected The low value for blood cholesterol was also against the diagnosis of chronic nephrosis with edema

Death occurred before a contemplated congo red test for amyloid disease could be carried out. Necropsy was performed nine hours after death.

*Necropsy*—Moderate edema of the lower extremities was present. The left pleural cavity contained 1,000 cc of clear, straw-colored fluid. The heart weighed 198 Gm. The spleen weighed 261 Gm, and was slate blue and of firm consistence. The cut surface was mottled by dark grayish, pinpoint markings, the remainder of the spleen appearing light red. Iodine gave the darker markings a reddish-brown hue. The liver was normal in appearance. Iodine, applied to the sectioned surface, failed to give an amyloid reaction. Beginning on the anterior wall of the greater curvature, 7 cm below the cardia, the stomach was involved in an extensive neoplastic process. The area involved almost the entire fundus. A few small, sessile, polypoid masses projected from the surface of the growth. The serosa along the greater curvature and the lymph nodes along the lesser curvature

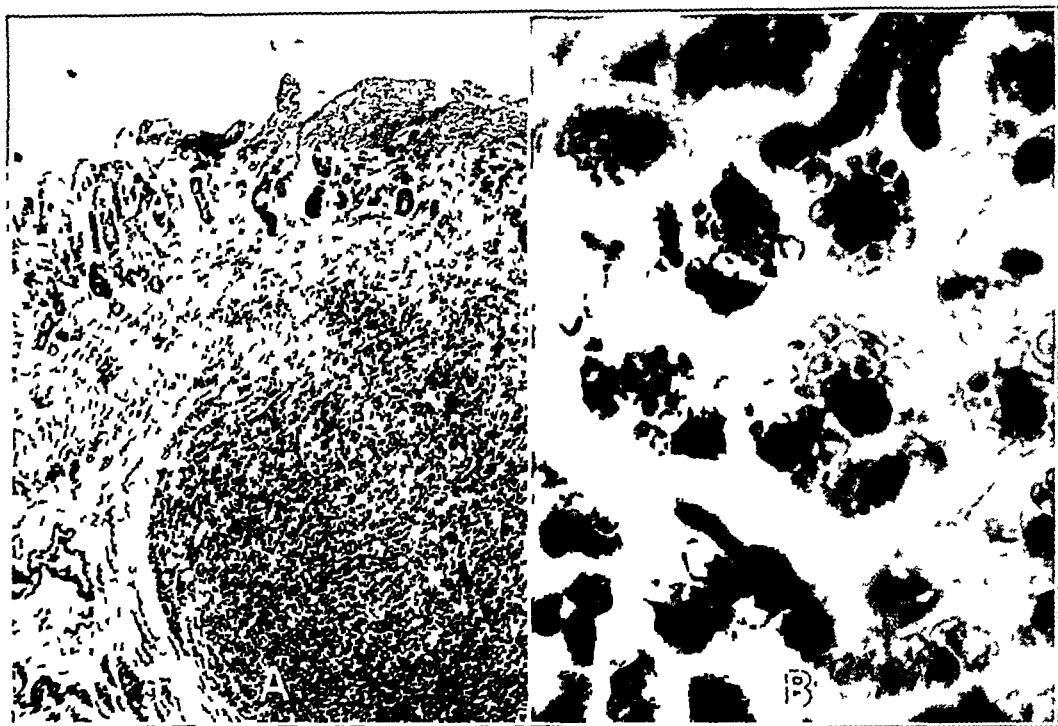


Fig 4 (case 3)—*A*, low power view of the gastric carcinoma, revealing the medullary and infiltrative characteristics, *B*, high power view of the gastric carcinoma. The acidophilic cells, containing eosinophilic granules, are well shown.

were involved. The cortex of the left suprarenal gland was atrophic. The right kidney weighed 160 Gm and the left, 201 Gm. An amyloid reaction was not elicited by iodine. The myocardium, stained with congo red for microscopic examination revealed, in many arterioles, a varying amount of hyaline, red-staining material. Occasionally, small amounts of a substance of similar appearance were observed in the stroma, and about these zones muscular atrophy was apparent. Sections of the spleen disclosed focal deposits of an eosin-staining, hyaline substance, situated in the zones of the malpighian corpuscles. In the sections stained with congo red, this hyaline material stained brilliantly red. By staining with methyl violet, the hyaline material appeared light red or pink. Iodine gave the hyaline deposits a reddish-brown hue. This color was not changed by the addition of sulphuric acid. The liver revealed hyaline, eosin-staining, homogeneous deposits usually about the periportal spaces or circumscribing the peripheral third of the

hepatic lobule (fig 3) With congo red, the hyaline replacements were observed to stain intensely red Methyl violet gave only a slight suggestion of the metachromatic reaction characteristic of amyloid Iodine, however, imparted to the substance a reddish-brown hue, which was neither intensified nor changed by the addition of sulphuric acid Sections of the gastric neoplasm disclosed an infiltrating, medullary type of carcinoma simplex, composed of large, rounded or polygonal cells, the cytoplasm of which was extensive and usually distinctly acidophilic A small amount of stroma and a few vascular channels completed the picture (fig 4A) Under higher magnifications, the cytoplasm of the acidophilic cells was seen to contain rather large, hyalin-like, eosinophilic granules (fig 4B)



Fig 5 (case 3) —Two glomeruli revealing deposits of amyloid

Mitotic figures were fairly numerous, or, as seen in other cells, the nuclei were large and hyperchromatic or undergoing retrogressive changes, such as pyknosis and karyorrhexis At the periphery of the growth the gastric mucosa was undermined by the malignant cells The muscular coats of the stomach and the serosa were involved The eosinophilic, cytoplasmic granules of the "acidophilic neoplastic cells" did not react with either iodine or methyl violet stain Throughout both suprarenal glands there was atrophy of the cortical parenchyma at the expense of intercellular hyaline deposits, which stained with congo red, as amyloid The kidneys disclosed only focal, hyaline thickening of glomerular tufts Congo red revealed this change as amyloid (fig 5) A few similar deposits were seen in the walls of the intertubular, renal blood vessels and stroma

The anatomic diagnosis was as follows (1) carcinoma of the stomach, probably of the acid-cell type, (2) generalized amyloidosis, involving the liver, spleen, kidneys and suprarenal glands, (3) hypoplasia of the heart (198 Gm, normal, 250 Gm) with calcareous deposits in the mitral valve, and (4) hydrothorax on the left side (1,000 cc) and slight edema of the lower extremities

#### COMMENT

*Clinical Features*—In case 1, a diagnosis of acute nephritis was practically excluded by the history and by the fact that the patient's condition was too grave to be explained by acute nephritis in the absence of a higher degree of renal insufficiency. Furthermore, the absence of edema and anemia, the presence of hypotension and the fact that the urine had a specific gravity of only 1.015, although loaded with albumin, were against such a diagnosis. Subacute or chronic glomerulonephritis was unlikely because of the low blood pressure and the absence of anemia, and because the patient was too sick for the degree of renal insufficiency that could be demonstrated. Chronic lipid nephrosis was easily ruled out by the absence of edema and the presence of hematuria. Pyelonephritis and acute toxic nephrosis were readily dismissed after momentary consideration.

We realized, then, that the data in this case were atypical for any of the ordinary forms of nephritis mentioned, and it was naturally deemed advisable to exclude other possibilities, such as Bence-Jones proteinuria with renal insufficiency<sup>3</sup> or amyloid disease, even though there was no reason to suspect the presence of either.

Bence-Jones protein was not present, but the congo red test for amyloid disease was strikingly positive, and after tests of hepatic function had indicated extensive involvement of the liver, the diagnosis of diffuse amyloidosis was correctly made.

Likewise, in case 3, the marked edema, the heavy albuminuria, the hypotension, the very low value for serum protein, with inversion of the albumin-globulin ratio, all suggested chronic nephrosis with edema. The low value for blood cholesterol, however, practically excluded lipid nephrosis, especially since there were other atypical features, such as slight anemia and an abnormal number of erythrocytes in the urine. Furthermore, the patient appeared too ill to allow a diagnosis of ordinary chronic nephrosis. This raised the possibility of a nephrotic stage of chronic glomerulonephritis, but he was too sick to allow of this diagnosis also, considering the normal values for blood urea and the normal rate of excretion of phenolsulphonphthalein, moreover, he had

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3 Bannick, E. G., and Greene, C. H. Renal Insufficiency Associated with Bence-Jones Proteinuria. Report of Thirteen Cases with a Note on the Changes in the Serum Proteins, *Arch Int Med* 44:486 (Oct) 1929.

hypotension rather than hypertension. A cardiac basis for his disability was easily excluded. The extremely low value for serum proteins aided in ruling out cardiac dropsy, for in this condition it would be normal or increased, the patient, furthermore, did not have a diuretic response to salyrgan that would have characterized cardiac dropsy. The direct van den Bergh reaction of the serum bilirubin suggested a hepatic basis for the ascites and edema, but, again, the low value for serum proteins, the marked albuminuria and the early occurrence of edema of the left arm, abdominal wall and other regions proved that other important factors were present.

The patient appeared cachectic, and the probability of malignancy was immediately considered, but this did not explain all the data. Therefore, final analysis of the history and data in this case suggested a diagnosis of a malignant condition, probably of the stomach because of the history, but this diagnosis was inadequate, it suggested a diagnosis of hepatic disease, but this also was inadequate and it suggested the diagnosis of nephrosis, which in its turn was inadequate.

The best explanation of the combination of conditions was that the patient had a malignant disease, with diffuse amyloidosis and amyloid nephrosis, this diagnosis was tentatively made, and a congo red test was requested for confirmation. We feel certain that this would have shown the characteristic response and resulted in a definite and accurate diagnosis.

In case 2 the diagnosis of diffuse amyloidosis was not made by any of the physicians who saw the patient in this clinic or in two large clinics elsewhere, yet all appreciated that they were dealing with an unusual case of hepatic disease of some sort, and those in attendance during the patient's terminal illness at this clinic observed that a combination of profound renal, suprarenal and hepatic insufficiency was manifested. By employing the same line of reasoning and exclusion as that outlined in cases 1 and 3, and as emphasized previously, diffuse amyloidosis might have been suspected, and a congo red test probably would have resulted in a correct diagnosis even though the etiology remained obscure.

We have felt justified in predicting that congo red would have disappeared rapidly from the blood stream in cases 2 and 3 because of the very extensive deposits of amyloid, and because of the striking reaction of these deposits to congo red after death. This conclusion we are sure, would have the approval of Bennhold,<sup>4</sup> who noted in his

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4 Bennhold, Hermann. Ueber die Ausscheidung intravenös eingegebenen Kongorotes bei den verschiedensten Erkrankungen insbesondere bei Amyloidosis, *Deutsches Arch f klin Med* **142** 32 (March) 1923.

early work on this subject that patients with extensive amyloidosis, especially amyloidosis of the liver, practically all gave positive congo red tests, and that it was when the deposits of amyloid were not extensive that one might obtain a negative congo red test. An abstract of our experience with this test, as applied to the diagnosis of amyloid disease, has been published previously.

*Pathologic Features*—The unusual features in case 2 were the development, without apparent cause, of diffuse, hyaline, amyloid-like deposits and also the character of the hyaline substance, which did not possess the usual specific staining qualities of amyloid. There were no evidences of suppuration or chronic disease, which are generally considered to be the prerequisites in the etiology of amyloidosis. The slight nodal enlargement, which suggested Hodgkin's disease clinically, did not resemble this entity pathologically. The staining reactions of the hyaline substance were never entirely characteristic for amyloid. In the fresh state the gross iodine reaction revealed a change in color to dark brown or black, never the typical reddish brown. In sections, the iodine reaction failed completely. The addition of sulphuric acid also failed to produce a response to the iodine reaction. Staining with methyl violet was partially successful, but failed to disclose the usual degree of metachromatic reaction given by amyloid. Staining with congo red demonstrated the deposits best, but this reaction is probably less specific than the other two. Other hyaline substances have marked affinity for the dye.

We may, therefore, conclude that in this case we were not dealing with true or chemically perfect amyloid, but rather with a hyaline, amyloid-like substance, possessing some and lacking other features of true amyloid, and yet best classified as amyloid.

The postmortem studies in case 3 revealed two interesting and unusual conditions: first, the peculiarities of the carcinoma of the stomach, and second, the generalized amyloidosis which was unassociated with suppuration or chronic disease other than gastric malignancy. The carcinoma had evidently been present for a long time. This fact may have significance in the pathogenesis of amyloidosis in this case. In its microscopic appearance, the malignant process was revealed as a medullary type of carcinoma simplex, with peculiar acidophilic staining of the cytoplasm of its cells. The amyloid in this case, unlike that in case 2, gave all of the typical staining reactions characteristic of amyloid. We may conclude from the staining reactions that the amyloid in case 3 was essentially of the same structure as deposits of amyloid usually are, and that its formation was in some way related to the gastric carcinoma.

## SUMMARY AND CONCLUSIONS

1 Two cases of diffuse amyloidosis of unusual etiology and one case of unknown etiology are reported. In case 1, the basis for the amyloidosis was probably Hodgkin's disease, and in case 3, an unusual type of gastric carcinoma.

2 The case in which the etiology was obscure, case 2, was also atypical pathologically, in that the amyloid-like deposits did not have all of the staining characteristics of ordinary amyloid.

3 The carcinoma in case 3 was a rare form of gastric carcinoma and suggested an acid cell type.

4 Diffuse amyloidosis usually can be diagnosed if suspected. The congo red test is a valuable laboratory aid in the diagnosis of this condition.

5 Amyloidosis should be considered in the differential diagnosis of all unusual cases of hepatic, splenic, renal or suprarenal disease, even though no apparent basis for amyloidosis is noted.

6 In each of the three cases reported, suprarenal insufficiency was noted clinically, and necropsy revealed extensive suprarenal amyloidosis. In each case hypotension was striking, and in cases 1 and 2 the crisis of Addison's disease was simulated, but in no case was there abnormal pigmentation.

## Book Reviews

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**Endocrine Medicine** By William Engelbach Volume I General Considerations Volume II The Infantile Endocrinopathies Volume III The Adolescent Endocrinopathies The Adult Endocrinopathies [Volume IV, containing Bibliography and Index, will be issued later] Cloth Price, \$35 per set Pp 460, with 138 illustrations, 473, with 214 illustrations, 862, with 366 illustrations Springfield, Ill Charles C Thomas, 1932

"When a man's knowledge is not in order, the more of it he has the greater will be his confusion" This is the embarrassing situation, certainly, in which most physicians have found themselves as regards the relation of the endocrine glands to medicine As a matter of fact, one wonders whether endocrinology as a workable "specialty" is destined to endure either in physiology or in clinical medicine Diabetes has long since and by common consent detached itself, because, as every one knows, special training in physiologic chemistry and in nutrition is necessary for the adequate handling of diabetic problems The endocrinology of the female is being preempted more and more by men with a sound gynecological background, the recent dramatic progress in the knowledge of disorders of the parathyroid gland comes from physiologically minded and chemically trained internists, and physiologists and general internists seem to be on the front line of the recent advances in the suprarenal problem So that stripped of its trappings little more remains than a straw man destined to be picked to pieces by the expert in heredity, in anthropometry and in chemistry, as well as by the surgeon, gynecologist and internist

It is with great interest, therefore that one approaches this latest work on endocrine medicine, and surely there is here a vast and valuable compendium of knowledge History, anatomy, physiology and chemistry, as well as more immediately practical matters, such as the methods of examination, clinical findings and treatment, are all dealt with at length The first volume on general considerations—"happy prologues to the swelling act"—is the most satisfactory, the later sections lose force because of the division into infantile, juvenile, adolescent and adult endocrinopathies, an arrangement which makes for repetition and offers difficulties in the pursuit of any single thread through the whole tangle One could also wish that the author had taken a more definite stand about certain matters, the reader is too often left to choose for himself from a variety of theories or modes of procedure, some of obviously doubtful soundness in the section on hyperthyroidism, for example one does not discover how the author really feels about the question of so-called toxic adenoma versus exophthalmic goiter With some of the "pituitary syndromes" and "gonadal syndromes," on the other hand, the reader, or at least the reviewer, is left confused as well as unconvinced that there is a sound basis for the claims of clinical classification To be frank, the reviewer is disappointed in the clinical sections No vivid pictures of disease appear, there is a disjointed assembly of ill-balanced material rather than a smooth and convincing story Furthermore the discussions, though lengthy, are often incomplete and inadequate On various occasions, for example, one is told that the differential diagnosis of a condition is made by ruling out other possibilities, but what these possibilities are or how they are to be excluded is not revealed But leaving aside such minor criticisms and turning to the positive merits of the work, there is an excellent collection of well illustrated and well documented case reports, even though the patient is often "put through the mill" and many of the tests have no bearing on the problem The format is attractive and does credit to Mr Thomas' interest in producing fine books

In these days when accurate and elegant use of words in medical writing seems to be considered of no special importance, one hardly knows whether to



comment on literary style but certainly the three graces of rhetoric—clearness, force and precision—did not assist at the birth of this compilation. The coining of new and impossible words to which the author frequently resorts, as well as the misuse of a word which resembles the one he evidently intended to use, is somewhat annoying, for example, rapid scientific “advancements” for rapid scientific “advances”, the “solicitation” of an anamnesis for the “eliciting” of an anamnesis, and the “purport” of this chapter for the “purpose” of this chapter. The statements that “relative unimportance will be placed” and that certain diseases are common in “juvenility,” as well as the reference to Roger of Palermo as “the Salernitan surgeon,” are disturbing to the language-conscious reader, and such a statement as “the measurements have been limited to seven, and, for the practical purposes of this Country, given in inches and the weight in pounds” (vol 1, p 265) is grammar so bad as to be beyond remedy. By “progesterol” effects, one supposes that the writer means “progestational” effects (vol 1, p 15).

**The Failing Heart of Middle Life. The Myocardosis Syndrome, Coronary Thrombosis, and Angina Pectoris, with a Section upon the Medico-Legal Aspects of Sudden Death from Heart Disease.** By Albert S. Hyman, A. B., M. D., F. A. C. P., Cardiologist, Beth David and Manhattan General Hospitals, Attending Physician and Cardiologist, Hospital for the Aged, Consulting Cardiologist, Harlem Day Nursery, Chief, Cardiac Clinics, Beth David and Manhattan General Dispensaries, Director, Witkin Foundation for the Study and Prevention of Heart Disease, New York, and Aaron E. Parsonnet, M. D., C. M., F. A. C. P., Attending Physician and Cardiologist, Newark Beth Israel Hospital, Cardiologist, Evening Heart Clinic, Newark Beth Israel Hospital, Medical Director, Home for the Aged. Fellow, Witkin Foundation for the Study and Prevention of Heart Disease, Newark, N. J. With a preface by David Riesman, M. D., Sc. D., F. A. C. P., Professor of Clinical Medicine, University of Pennsylvania School of Medicine Philadelphia. Cloth Price, \$5. Pp 538, with 166 illustrations. Philadelphia F. A. Davis Company, 1932.

The increasing incidence of degenerative heart disease and its encroachment on the younger age groups have impressed every one who comes in contact with diseases of the heart. The present work deals with this type of disorder. Although the work is entitled “The Failing Heart of Middle Life,” the authors have determined the period of middle life, not by the calendar, but by the condition of the coronary arteries. The book is somewhat unique in that it deals largely with the type of disorder that is not the result of disease but of degenerative processes. The patients described were free from trouble until a diminished cardiac function appeared. To this condition they have applied the term the myocardosis syndrome, by which they distinguish it from heart disease of inflammatory origin. They stress further the importance of searching for certain signs and symptoms by which the degenerative process may be discovered before heart failure becomes a prominent symptom.

The book is divided into six sections. The first deals with the normal and pathologic coronary arterial system. This section is well supplied with photographs, photomicrographs and diagrams illustrating the coronary circulation in health and disease. The original work of Dr. Yaguda adds much to the value of this section.

The second part defines and describes the myocardosis syndrome.

The third part deals with thrombosis of the coronary arteries. The symptoms, findings, complications, prognosis and treatment are adequately considered.

Electrocardiographic changes due to coronary disease are considered in the fourth part. In such a debatable field as this, one which is undergoing daily revisions and modifications, statements will be found that will not meet with universal endorsement. The discussion, however, is excellent, and no major criticism may be offered.

Angina pectoris, another debatable and complex subject, is discussed in part five.

Part six is another unique feature, a medicolegal discussion of sudden death from heart disease. This section is interesting and very likely valuable, but it is beyond the reviewer to comment on its accuracy.

A bibliography of about 1,250 references completes the work.

The book is well written and readable. It will have a special appeal to the student and the general practitioner, to whom it is highly recommended.

**Organs of Internal Secretion** By Ivo Geikie Cobb. Fourth edition. Price, \$3.50. Pp 303. Baltimore: William Wood & Company, 1933.

This book first appeared in 1916. It is presumably a presentation of the latest known facts concerning the glands of internal secretion, but as has happened so often in books of this kind, there is no sharp distinction drawn between facts and fancy, nor is the book in any way a critical exposition of endocrinology. A few excerpts picked at random will illustrate this. On page 144 the statement is made that "the present writer has been utilizing padutin in a limited number of cases of arterial hypertension and it appears to produce a lower blood pressure with increased comfort to the patient." On page 160 it is stated "that the mammary gland extract is capable of stopping excessive menstrual flow and will also remedy too frequent menstruation." On page 165, quoting from another author, "a course of treatment of testicular extract frequently accomplishes such a number of changes of such remote organs, and influences such widely disconnected ones, that to report actual results might even be sufficient to discount the position of this method. There are a few single remedies which can compare with active and properly prepared testicular extracts." On page 169 it is stated that "many pluriglandular preparations contain an extract of one of the gonads as a component part. Many manufacturers are now placing on the market standardized solutions for hypodermic or intramuscular use. Where it is feasible, it is a more direct, and probably a more efficacious, method to administer these substances by the hypodermic route." On page 235 one finds, "for the neurasthenic patient, the extracts of the gonads, either alone or combined with extracts of nervous tissue, are frequently of great help." Pluriglandular preparations are recommended here and there throughout the book for the treatment of many conditions. "A general endocrine tonic will contain extracts of nervous tissue with perhaps a small dose of thyroid and pituitary and some orchitic or ovarian tissue." These quotations exemplify the absence of a critical attitude in presenting the subject matter. In the expressions of endocrine disorder the book may be considered reasonably sensible, but in the question of therapy, the realms of fancy are certainly reached. The most recent work of Collip, Hartmann, Doisy, Rogoff and others is merely mentioned. Very little attention is paid to the latest important studies of the female sex hormone, about a third as much is paid to the male gonads. Many of the statements made by the author are compiled from the literature of manufacturing houses and endocrinologic quacks, indicating the type of book that is being reviewed. It cannot be recommended.

**Clinical Diagnosis: Physical and Differential** By Neuton S. Stern, M.D., Associate Professor of Medicine, University of Tennessee School of Medicine. Price, \$3.50. Pp 364. New York: The Macmillan Company, 1933.

Many a clinician, in the depths of his heart, feels that some day he will write the most perfect volume on clinical diagnosis ever put forth. Therefore, because of this feeling, he may appear to be unduly critical of new books on this subject as they appear from time to time.

Dr. Stern's "Clinical Diagnosis" is a nice appearing volume of convenient size and it is well printed. It is written logically and clearly and contains a great deal of sound information. Anatomically, it is divided into four parts. The first deals with the taking of a history and physical examination, seven pages being devoted to the former topic and more than a hundred to the latter.

The second part deals with symptoms and signs in pulmonary tuberculosis and cardiac disease, only ten pages being devoted to the subject of tuberculosis and more than fifty to the heart

The third part deals with the principles and practice of differential diagnosis, and includes a series of twenty-one "paper cases" These can be utilized in class-work according to the method found successful by Dr Richard C Cabot about twenty-five years ago

The fourth part is a short glossary and defines with more or less detail about one hundred medical expressions and terms Of this part, the most ingenious bit is a description of the interpretation of electrocardiograms, with a schematic representation of what a normal tracing looks like and of the abnormalities most commonly encountered

Critical-minded folk, perhaps, will hope to see the second edition of this book lay more emphasis on the taking of a history and less on cardiovascular examination, more on the fact that careful pelvic and neurologic examinations should be considered as a part of a general physical examination and less a special one But these, after all, are minor weaknesses Without doubt the book is a good one, and will prove helpful to students

**Biochemistry in Internal Medicine** By Max Trumper, Ph D, and Abraham Cantarow, M D Price, \$5.50 Pp 454 Philadelphia W B Saunders Company, 1932

This book is intended to supply the physician or the medical student with an interpretation of the biochemical methods used in routine and more exacting laboratory studies It is a good bridge over the gap between the clinical and the more abstract biochemical studies The authors rarely refer to the actual laboratory procedures, but emphasize the interpretations and applications of the results found by the modern methods The metabolism of carbohydrates, proteins, cholesterol, chloride, calcium and phosphorus is presented in a concise and clear manner with possibly too little criticism of the true absolute values of the quantities reported by different methods in some estimations Cholesterol is referred to as "a mixture of two or more sterols" Acid-base balance is presented in a clear and readable style with emphasis on the more important mechanisms involved in the control of the  $pH$  of the blood The method followed in attempting to explain the  $pH$  may be questioned Naturally much of the material mentioned is again presented in an organized scheme under the discussion of basal metabolism, diabetes mellitus, renal function, nephrosis, hepatic function, gastric function, pancreatic function, changes in pregnancy and lactation and composition of cerebrospinal fluid, transudates, exudates and edema fluid The usual miscellaneous chemical findings on urine are dealt with, and finally the reader is supplied with normal values on various body fluids and an outline enumerating chemical changes associated with various clinical diagnoses

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